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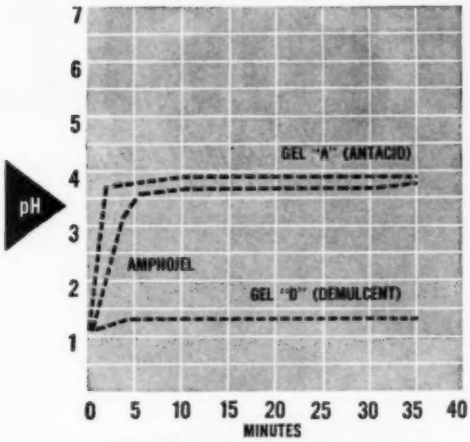

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*Rakoff, A. E.; Paschkis, K. E. and Cantarow, A.: A Clinical Evaluation of Dienestrol, a Synthetic Estrogen, J. Clin. Endocrinol., 7:688-700 (Oct.) 1947.

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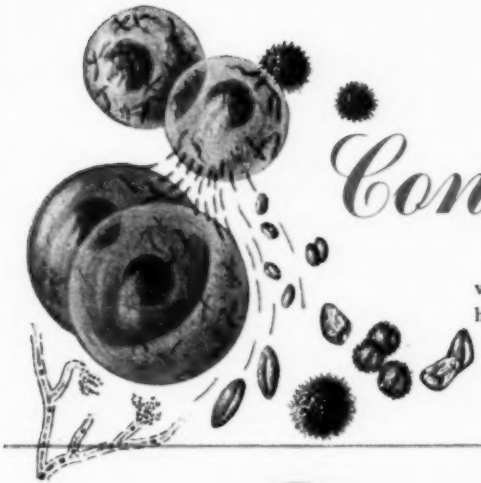

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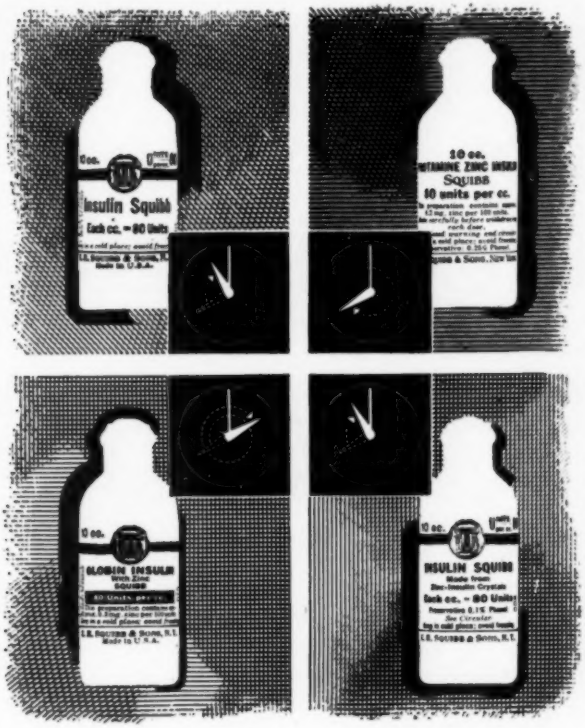

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THE PROTHROMBIN TIME IN DICOUMAROL THERAPY *

By F. C. COLEMAN, M.D., *Des Moines, Iowa*

THE identification of dicoumarol as the cause of sweet clover disease was made by Link in 1939. This disease is a hemorrhagic disease in cattle which have eaten spoiled sweet clover, and is due to a decrease in the prothrombin content of the blood. In 1941 Link reported the synthesis of dicoumarol. It could be prepared in large quantities at low cost. Within three months the first published report of its clinical use was made by Allen, Barker and Waugh. It is of therapeutic value in those diseases where intravascular clotting is present. These are, particularly, thrombosis and embolism following operation, trauma, infection or childbirth. Recently it has been used in congestive heart failure with venous or mural thrombosis and in coronary occlusion. Administration as a prophylactic measure against thrombosis following operation or childbirth has been recommended. In these cases the dicoumarol is started on the first to third postoperative or postpartum day.

The clotting of blood is thought to take place in two stages. In the first stage there is a conversion of prothrombin to thrombin in the presence of calcium and thromboplastin. In the second stage the thrombin unites with fibrinogen to form fibrin. Fibrin acts as the supporting framework for the platelets, red cells, and white cells present in a clot. Prothrombin is formed in the liver from vitamin K. Thromboplastin is present in the platelets and tissue juices, being particularly plentiful in the brain and lung. Calcium and fibrinogen are present in the blood plasma.

To prevent blood from clotting, at least one of the factors in the clotting mechanism must be removed or inactivated. We use potassium oxalate as an anticoagulant in the laboratory because it unites with the calcium of the plasma to form the inactive salt calcium oxalate. Thus, no calcium is free to assist in converting the prothrombin to thrombin. Blood does not

* Presented before the State Divisional Meeting of the American College of Physicians in Des Moines, Iowa on September 27, 1947. Received for publication February 12, 1948.
From the Department of Pathology, Mercy Hospital, Des Moines, Iowa.

clot normally inside the blood vessels because of the movement of the circulation, the absence of free thromboplastin, and the presence of small quantities of antithrombin and heparin in the plasma. When conditions are such that intravascular clotting might occur it can be prevented by dicoumarol administration. Dicoumarol prevents intravascular clotting by decreasing the prothrombin content of the plasma. This is done by inhibiting its formation in the liver. None of the other functions of the liver are interfered with. Although prothrombin formation is stopped almost immediately, the prothrombin already present in the plasma must be exhausted. This accounts for the 24 to 48 hour lag in effect of the dicoumarol on blood clotting. It is obvious that the dosage of this drug must be controlled in some way. Since its action is to decrease prothrombin, the logical step would be to measure the amount of prothrombin present in the plasma. This cannot be done by exact chemical methods such as those used in determining the concentration of calcium or phosphorus. The clotting time of blood, however, is proportional to the amount of thrombin present when calcium, thromboplastin and fibrinogen are present in adequate amounts. Under normal conditions the amount of thrombin formed in turn is proportional to the amount of prothrombin present in the blood. All methods for determining the prothrombin time, then, are based on measuring the clotting time when calcium, thromboplastin and fibrinogen are present in adequate amounts. Approximately three-fourths of the clotting time is taken up in the conversion of prothrombin to thrombin, and the other one-fourth in the formation of fibrin from thrombin and fibrinogen.

Methods for determining the prothrombin time may be divided into two groups: (1) Those performed on plasma; (2) Those performed on whole blood.

Those performed on plasma include the Quick method and all of its modifications. Oxalated venous blood is used. An exact amount of calcium is then added to the plasma, as well as an excess of thromboplastin. The thromboplastin used may be of two types. In the original Quick method thromboplastin prepared from rabbit brain was suspended in normal saline. The clotting time of normal plasma was 18 to 22 seconds. A decrease in prothrombin content was indicated by an increase in the time necessary for clotting to take place. This method gave rise to the term "prothrombin time," for the results actually were expressed in terms of seconds.

Subsequently, Quick extracted the rabbit brain with acetone. This gave a much more potent thromboplastin which produced clotting in normal plasma in 11 to 12 seconds. The results are reported in terms of prothrombin concentration rather than in seconds. To calculate the prothrombin concentration normal plasma is diluted serially with saline from 100 per cent to 5 per cent. As the plasma is diluted the prothrombin content is decreased. Prothrombin determinations are then made on the normal plasma and all of the dilutions. The results are expressed graphically.

From this graph the prothrombin content of the patient may be expressed in terms of the dilution of normal plasma containing this amount. This is known as the prothrombin concentration. Quick also devised a formula by which the same results may be obtained without using the graph.

Stewart and Pohle modified Quick's method slightly by varying the amount of calcium. By using acetone extracted rabbit brain as a source of thromboplastin they were able to get a clotting time of as low as 10 seconds on normal plasma. The results are expressed in terms of prothrombin concentration just as in the second Quick method. Both methods have the disadvantage of showing considerable variation if an error of even one second is made in recording the clotting time.

The Magath modification of the Quick method is used at the Mayo Clinic. Saline suspensions of thromboplastin prepared from rabbit brain are used, but each batch is carefully standardized. Those thromboplastins which give a normal clotting time of 17 to 19 seconds are saved. These are then set up against serial dilutions of normal plasma. Only those which give a clotting time of 27 seconds with the 30 per cent dilution, 35 seconds with the 20 per cent dilution, and 60 seconds with the 10 per cent dilution are used. Since by this method a 20 per cent prothrombin concentration is considered to be optimum in dicoumarol therapy, 35 seconds is used as the guide for ordering or withholding the drug.

The Fullerton modification of the Quick method utilizes viper venom as a source of thromboplastin instead of rabbit brain. The results are reported in the same manner as in the second Quick method. In the Link modification of the Quick method a 12.5 per cent dilution of plasma is used instead of whole plasma.

There are two methods in which the determinations are performed upon whole blood. The one most commonly used is the Smith bedside technic. This method is technically the easiest to perform, and, as the name implies, can be done at the bedside of the patient. Thromboplastin prepared from ox lung is diluted with normal saline so that when added to normal blood it will clot in 25 to 30 seconds. No calcium is added, the calcium of the plasma being considered adequate. Whole venous blood is added to the thromboplastin and the tube tilted back and forth until clotting takes place. The same procedure is then repeated on a normal control. The clotting time of the control in seconds, divided by the clotting time of the patient in seconds, gives the prothrombin time of the patient in percentage of the normal control. This method has been criticized as being too insensitive for use in controlling dicoumarol therapy. These criticisms are based on the fact that whole blood is used rather than plasma. Since prothrombin is present in the plasma only, variations in the hematocrit will alter the amount of prothrombin in a measured quantity of blood.

The micro method of Kato and Poncher is similar to Quick's method except that a drop of oxalated blood secured from a finger puncture is used

instead of oxalated plasma. The test is always performed at room temperature. The results are expressed in terms of the prothrombin concentration.

Other methods which have been described include the Smith two-stage technic and the method of Dam and Glavind. These are not in clinical use.

It is obvious that marked confusion may arise in the interpretation of a prothrombin report unless one knows the method which has been used. As an example—a patient with the same amount of prothrombin in the blood might be reported as having: (1) A prothrombin time of 25 seconds (Quick's method, original); (2) A prothrombin of 60 per cent expressed in terms of prothrombin concentration (Stewart and Pohle); (3) A prothrombin of 45 per cent expressed in terms of prothrombin concentration (Magath modification of Quick's method); (4) A prothrombin of 72 per cent of normal (Smith bedside technic). How then are we to know what the prothrombin report means when it is noted on the patient's chart? It is essential that one method be standard in each laboratory and that the Staff knows the method which is being used. It is extremely important that only one technician be assigned to perform prothrombin determinations. For this reason we do not run them on Sundays except in cases of emergency. Even with the same technicians running the tests the technical error is around 10 per cent.

A good schedule to follow on any patient who is to receive dicoumarol is as follows: Have a prothrombin determination made. Then, give 300 mg. of dicoumarol by mouth. Guide further therapy with daily prothrombin determinations. When the prothrombin is above 20 per cent of normal using either the Quick method or the modifications of Magath, Stewart and Pohle or Kato and Poncher 100 to 200 mg. of dicoumarol may be given. If the prothrombin is less than 20 per cent it should be withheld. If the prothrombin is less than 40 per cent of normal using the Smith bedside technic, dicoumarol should be withheld. If it is above 40 per cent, 100 to 200 mg. may be given.

The response of the patient to dicoumarol varies considerably. Vitamin C deficiency enhances the effect of the dicoumarol. Salicylates should never be given at the same time as dicoumarol because they also enhance the anticoagulant effect. This is particularly true of aspirin. Dicoumarol is chemically related to salicylic acid and a dicoumarol-like action may be produced by administration of large doses. Patients with severe renal or liver damage should never receive dicoumarol as the anticoagulant effect is exaggerated. Caffeine, theophyllin and theobromine on the other hand tend to nullify the action of dicoumarol. This is probably due to a stimulation of the liver to produce prothrombin. The tendency of these drugs to increase the clotting ability of the blood is of importance in coronary disease. Here thrombosis may be accelerated.

Heparin is frequently started at the same time as dicoumarol and con-

tinued for the 48 hour period necessary for dicoumarol to take effect. This is done because most emboli come from thrombi which are less than 48 hours old. Since the dicoumarol is not given to resolve thrombi already formed but to prevent thrombus propagation and embolism this appears to be a rational procedure. Heparin seriously interferes with prothrombin determinations, however, and these should never be done within three hours after heparin has been given. The effect of heparin has disappeared after this time and true readings will be obtained.

Dicoumarol therapy would be very dangerous if there were no way to counteract its effects. Recent studies have shown that the prothrombin content of the blood may be returned to normal within 24 hours by administration of large doses of vitamin K intravenously and by the administration of whole blood transfusions. The dosage of vitamin K usually recommended is 60 mg. of menadione bisulfite intravenously every eight hours.

The prothrombin content of bank blood decreases rapidly so that it may be 50 per cent in blood a week old. Fresh blood, therefore, is preferable to bank blood. If bank blood is used, it should not be more than 48 hours old. Since vitamin C deficiency enhances the dicoumarol effect, large doses of vitamin C should be given when prothrombin content is being returned to normal. These measures are applicable to patients who show excessive bleeding or in those on whom surgery is necessary.

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EARLY DIAGNOSIS OF CARCINOMA OF THE STOMACH *

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Carcinoma of the stomach continues to be the foremost cause of cancer deaths. Despite improvements in diagnostic and surgical technics, five year survival rates have not been altered appreciably [1, 2] in the past 10 years, and there is no reason to believe that they will be in the future.

The increased use of roentgen-ray and gastroscopic examination have led to more frequent diagnoses of gastric carcinoma but not to increased cures. All of our present diagnostic methods depend on the patient presenting himself because of symptoms. Due to the silent nature of the disease, the symptoms are rarely severe enough to bring the patient to the physician until the tumor has become widespread.

The lesion is present for an unknown period before the patient becomes aware of any physical derangement. The earliest symptoms fail to form a recognizable syndrome. If the physician depends on established diagnostic criteria, he will rarely discover an early malignancy of the stomach.[3]

In an effort to discover any findings that might lead to earlier diagnosis, 109 cases of gastric carcinoma diagnosed at the State University of Iowa Hospitals in 1941 and 1942 were analyzed. Search was made for any information that might lead to the use of roentgen-ray examination of the stomach earlier in the course of the disease, and also for any findings that might indicate resectability prior to operation or might aid in predicting survival.

Analysis

Sex and Age Incidence. Of the patients with gastric carcinoma that came to the State University of Iowa Hospitals in 1941 and 1942, 91 were men and 18 were women, the ratio being five to one. Although females composed only 16 per cent of the group, they made up 33 per cent of the survivors over two and a half years. The majority of cases occurred between the fiftieth and seventieth years.

Presenting Symptoms. The outstanding features of the presenting symptoms were their vagueness and insidious onset. None of the first symptoms suggested the serious nature of the disease, and with few exceptions they were compatible with those of so-called functional disease of the gastrointestinal tract.

Vague epigastric distress was the most common presenting symptom and ranged from "bloating," "fullness," or "indigestion" to actual pain. Weight

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loss frequently antedated all symptoms but was so gradual in development that its significance was not apparent until late. Weakness was commonly reported. Several patients described decreased gastric capacity, saying that they "couldn't eat much at a time."

Symptoms simulating the ulcer syndrome, including relief of pain on taking food or alkalies and tenderness to palpation, occurred in 11 cases.

FIG. 1. A film of the abdomen taken five hours after the ingestion of barium demonstrates the delicacy and uniformity of the mucous membrane markings in the normal small bowel. The even distribution of the barium and regular caliber of the small bowel is shown.

This was not necessarily associated with an ulcer type of defect. Constipation was the presenting symptom in about 15 per cent of the cases, sometimes occurring in the absence of epigastric distress. Diarrhea was frequently reported.

The textbook symptoms of anorexia and vomiting were almost com-

pletely absent until late in the disease. Five of the patients reported a good appetite. Other presenting symptoms were sore tongue, dysphagia, back pain and nervousness.

Duration of Symptoms. The average duration of symptoms was 11 months with extremes of four weeks and five to six years. The duration of symptoms was no indication of the extent of tumor growth. Of 23 cases with as short a history as three months or less, 17 had wide dissemination of the lesion, making curative surgery impossible. Representative cases are included in table 1.

TABLE I

Extent of Disease in Cases with Short History

Age of Patient	Sex	Duration of Symptoms	Presenting Symptoms	Extent of Disease
51	M	4 weeks	Regurgitation shortly after eating. 30 to 40 lb. weight loss.	Cardiac end of esophagus and stomach.
59	M	10 weeks	"Flu" and diarrhea. Black stools.	Involvement of pylorus with extensive peritoneal seeding.
36	M	2 months	Pain in epigastrium. Retention of food. 13 lb. weight loss.	Virchow's node. Palpable epigastric mass, large gastric filling defect.
69	M	2 months	Gas, bloating, epigastric pain and fatigue.	Marked involvement in pars media. Implants in mesentery and lymph nodes.
58	M	2 months	Stomach distress. 10 lb. weight loss. Decreased gastric capacity.	Distal half of stomach infiltrated. Omental and retroperitoneal nodes.
71	F	2 months	30 lb. weight loss. Weakness and fatigue.	Elevated neoplasm 2½ inches in diameter with early ulceration. No nodes.
61	M	3 months	Discomfort, bloating.	Widely disseminated beyond regional nodes and involvement of pylorus and pars media.
44	M	3 months	Weakness and weight loss.	Lung, liver and peritoneal metastases. Filling defect in pylorus.
56	M	3 months	Epigastric distress; bloating.	Filling defect involving antrum. Metastases to posterior cul de sac.
71	M	3 months	Vomiting, weakness and 25 lb. weight loss.	Filling defect of lower two-thirds of stomach. Virchow's node.

Physical Findings. Of the physical findings, cachexia was most frequently reported, being described in over 64 per cent of the cases and probably present in many more. Epigastric masses were palpable in but 35 per cent of the patients although some may have been masked by rigidity of the abdominal wall in an additional 20 per cent. Paleness was noted in 23 per cent of the cases. The epigastrium was tender to palpation in 18 per cent. Virchow's nodes were felt in 6 per cent; Blumer's shelf in 14 per cent; abdominal distention or ascites in 4 per cent with one case each of pleural and osseous metastasis; making a total of 26 per cent with evidence of widespread

neoplastic metastasis on entrance examination. The liver was palpable in only 15 patients.

Survival Related to Treatment. A curative operation was attempted in every case in which the involved portion appeared resectable. This included cases with extension to the pancreas, mesocolon and esophagus, in addition to those limited to the stomach and regional lymph nodes.

Sixty-six patients, or 62 per cent, were operated upon at this hospital with an overall surgical mortality of 15 per cent. Surgical deaths were excluded when calculating average survival periods.

Thirty-one per cent of those patients surviving a curative procedure were still living after five years.

Those surviving a palliative operation lived about two months longer than those patients who had only an exploration or no surgical treatment.

FIG. 2a. A film taken shortly after ingestion of barium shows a nodular, exophytic filling defect at the pars media. The mucosal pattern of the duodenum and jejunum is well demonstrated and appears normal.

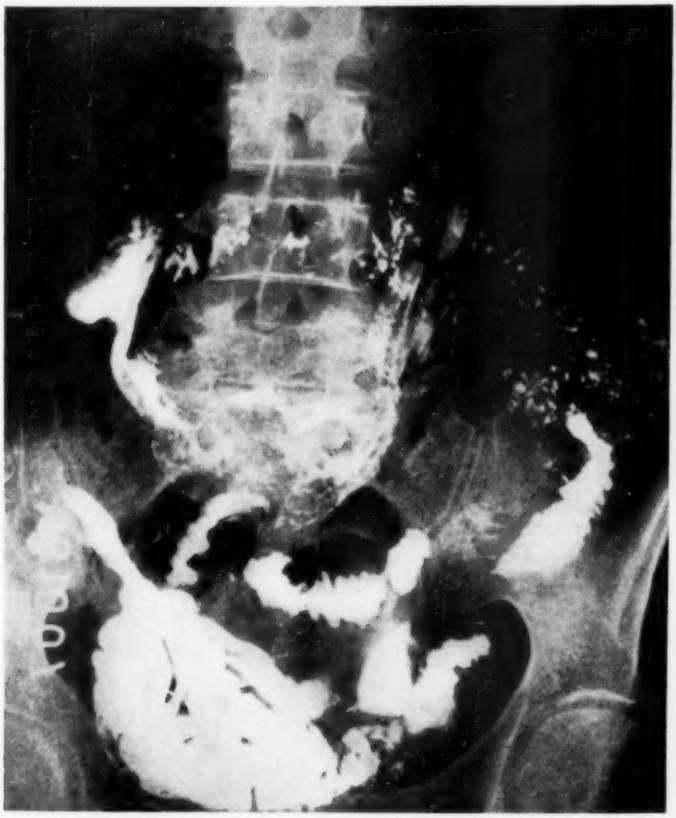

FIG. 2b. Five hours after the ingestion of barium, the head of the meal has advanced to the distal ileum, portions of it lying scattered through the jejunum and clumped in the proximal ileum, which shows hypersegmentation. The mucosal folds in the proximal ileum appear coarsened, due to edema incident to hypoproteinemia.

One patient, diagnosed by roentgen-ray and gastroscopic examination as having carcinoma of the stomach, refused operation and remained alive and well for over five years. Review of his films suggests that the correct diagnosis was giant rugal folds, and the case was excluded from the series.

For the group as a whole regardless of treatment, 77 per cent were dead in one year, and 92 per cent by three years. Those alive at this time continued to be alive and well at five years. The five year survival rate of 8 per cent approximates the figures reported by most American clinics.

Survival Related to Degree of Involvement. At operation, the lesion was found to be limited to the stomach in only 11 patients and these had an

average survival of 53 months, seven of the patients being still alive and showing no evidence of recurrence after more than 60 months. The lesion was limited to the stomach and regional nodes in 15 patients or 14 per cent. Only two of these patients are alive after five years and an additional one could not be traced after two years. Fifty-eight per cent were known to have widespread metastasis and local extension.

TABLE II

Surgical Evidence of Disease Compared with Clinical Findings

Widespread Metastases		26%
Virchow's node	6%	
Blumer's shelf	14%	
Ascites	4%	
Pleural metastasis	1%	
Osseous metastasis	1%	
Clinical Evidence of Limitation to Stomach and Regional Nodes		74%
Surgical Evidence of Limitation to Stomach and Regional Nodes		24%

Laboratory Findings. Anemia was a prominent finding, as was depression of the plasma protein levels. This occurred in spite of a masking effect produced by chronic dehydration. Mellors and Abbott [4] have shown that the circulating plasma volume is decreased in the course of this disease. The values were calculated on admission, before the patient had time to become hydrated. Nevertheless, the hemoglobin was below 11 grams in 63 per cent

FIG. 3a. A film taken shortly after ingestion of barium shows an irregular filling defect involving the antral and pyloric portions of the stomach. The duodenal and jejunal mucosal patterns appear normal.

FIG. 3b. A film of the abdomen taken five hours later shows the major portion of the meal in the distal ileum. Some of the barium remains in the proximal ileum, where it exhibits hypersegmentation. The caliber of the ileum is variable, some of the segments being dilated.

of the cases, and the red cell count below 3.8 million in 52 per cent. One of the most consistent findings was depression of the plasma protein levels, the total protein being below 6.0 grams in 78 per cent; plasma albumin, 4.0 grams or less in 100 per cent; and plasma globulin below 2.5 per cent in 65 per cent.

The anemia was of variable types, and not limited to the hypochromic normocytic type typical of chronic minor hemorrhages. Many of the red cells displayed poikilocytosis and anisocytosis. Rhoads and his group[5, 6]

feel that the anemia associated with gastric carcinoma represents a blood dyscrasia based on a failure of transfer or storage of a gastric anti-anemic factor, into the liver. Liver damage seen in hypoproteinemia also contributes to poor blood regeneration.

TABLE III
Survival Related to Treatment

Procedure	Cases	% Distribution	% Surgical Mortality	Average Survival in Months
Curative	29	27	10	35*
Palliative	13	12	23	8
Exploratory	26	23	15	6
No surgery	41	38	—	5

* Nine patients alive and well 60 months following operation.

Anacidity and hypoacidity after histamine were frequent findings, being present in 79 per cent of the cases tested. Some cases had free acid, even in excessive amounts. This was true of the smaller lesions.

Roentgen-Ray Findings. In our experience, like that of others,[7] the roentgen-ray examination was the most definitive of all diagnostic methods. One hundred and five of the cases received an upper gastrointestinal examination, and carcinoma of the stomach was diagnosed or suggested in 96 patients or 91 per cent. Of the nine errors, two were diagnosed as benign ulcers, and one lesion was described as carcinoma in the duodenal loop rather than the stomach. The other six were called normal stomachs.

Most of the lesions occurred in the antrum and occupied both lesser and greater curvatures. Carmen's meniscus sign was observed in only four of 96 examinations. Foreshortening of the lesser curvature was a frequent observation.

TABLE IV
Survival Related to Degree of Involvement

	Cases	Per Cent Distribution	Average Survival in Months	5 Year Survivals	Per Cent
Limitation to stomach	11	10	53	7	64
Limitation to regional nodes	15	14	22	2	13
Widespread metastases and local extension	63	58	4	0	0
Unknown degree of involvement	20	18	8	0	0

The roentgen-ray appearance of a lesion could not be used as an index of resectability. Large filling defects sometimes had limited extragastric extension, while small ones were found to be widely disseminated at operation.

The small bowel displayed disturbed motor physiology in 58 per cent of the cases, as judged from films taken immediately and five hours after the

ingestion of barium. The duodenum and proximal jejunum always appeared normal but clumping, segmentation, and mucosal edema were observed in the distal jejunum and ileum. Transit time was ordinarily normal.

Whether the small bowel disturbance was the cause or the effect of avitaminosis and hypoproteinemia associated with malignancy is a matter of conjecture. It is known that vitamin B complex is poorly absorbed in the presence of decreased gastric acidity.[8] Lack of vitamin B is one cause of disturbed small bowel pattern, perhaps leading to failure of absorption of essential food elements. Mucosal edema due to hypoproteinemia adds to the deranged small bowel function. The relationship of this finding to the anorexia and cachexia of malignant disease should be investigated.

Discussion

This study indicates that in order to cure a reasonable number of patients, gastric resection must be done while involvement is limited to the stomach. Extension beyond this, even when limited to the regional nodes, causes a sharp drop in survival rate.

While our present diagnostic methods are capable of diagnosing gastric malignancy at a curable stage, the patients rarely present themselves at such a time. There were no symptoms that could be correlated to the curable type. With one exception, every patient with physical findings beyond weight loss was dead in five years; this one patient had a palpable movable epigastric mass.

It is evident that carcinoma of the stomach must be found while it is still asymptomatic. Dailey [9] and St. John [10] have conducted wide scale roentgen-ray screening experiments on symptomless males in the cancer age group. Dailey failed to find any gastric carcinoma in 500 men over 45. St. John found the incidence of gastric malignancy to be 1.24 cases per thousand, which is too low an incidence to make this type of examination practical as a screening procedure.

In order to select a group more likely to have a higher incidence, Rigler [11] limited his screening examinations to patients known to have possible precursors of gastric carcinoma—achlorhydria, a chronic gastritis, pernicious anemia, gastric polyps or a family history of carcinoma of the stomach. Wangensteen [12] followed a group, using the same indications and in addition, examined all patients with occult blood in the stools, unexplained anemia below 11 grams of hemoglobin, lingual mucosal atrophy or severe pyorrhea alveolaris. Both investigators found carcinoma in percentages far beyond the natural occurrence. Yet, though these cases were discovered earlier, only a few were still at a stage of development at which a cure was possible. Further, a complete physical and laboratory examination is necessary in order to select suitable candidates for investigation, making such methods too expensive and time consuming to extend to the entire cancer vulnerable popu-

lation. Routine photofluorographic examination of the stomach is being tried experimentally but it is unlikely that any but the larger lesions will be discovered in this manner.

The Papanicolau smear technic [13] has been adapted to gastric aspirations and can be used as an adjunct in all cases having gastric analysis or gastroscopy. Cell detail is surprisingly well preserved despite exfoliation into digestive juices; however, even in Papanicolau's hands, a high percentage of cases were missed because of poor cell preservation and the failure of scirrhous carcinoma to shed cells. Further, the requirement of gastric aspiration makes this method undesirable as a screening procedure.

Present methods are not adapted to the diagnosis of carcinoma of the stomach at a stage at which the majority of cases can be cured. A new medium of diagnosis must be discovered before five year survival rates can be increased.

Lacking new methods, the present methods should be used more extensively. A roentgen-ray examination should be given to every patient with even the vaguest gastrointestinal complaints. All asymptomatic individuals known to have possible precursors of gastric cancer should receive roentgen-ray examinations twice yearly.

All gastric ulcers, and cases of pyloric obstruction should be examined gastroscopically. Gastric ulcers which fail to heal on adequate medical management should be regarded with deep suspicion. Partial healing cannot be considered evidence of the benign nature of an ulcer, as malignant ulcers can fill in, as shown by Palmer and Humphreys,[14] and Eusterman.[15] Allen [16] reports that during a 10 year period at the Massachusetts General Hospital, 14 per cent of the patients given a medical treatment for benign ulcer actually had a malignancy, as proved by surgical and autopsy findings.

Summary and Conclusions

1. The innocuous nature of presenting symptoms of carcinoma of the stomach is emphasized. The delay in diagnosis after onset of symptoms averaged 11 months.

2. The physical findings are misleading, in that they suggest that the extent of the lesion is far more limited than it is found to be upon exploration.

3. Roentgen-ray diagnosis was accurate in 91 per cent of the cases.

4. A five year survival rate of 8 per cent is reported. Cures occurred almost exclusively in cases with involvement limited to the stomach, despite the use of an attempted curative operation in more extensive types.

5. Depressed plasma protein levels, particularly albumin, and an abnormal small bowel pattern are frequent findings.

6. The duration of symptoms and the roentgen-ray appearance of the lesion could not be correlated to the extent of involvement or survival period.

7. None of the present diagnostic methods are practical in increasing the detection rate of carcinoma of the stomach at a stage in which a reasonable chance of cure exists.

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FACIAL PAIN *

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FOR some time we have been amazed at some of the unusual concomitants of dental disorders, especially with reference to the cause of pain so frequently seen in and around the face. The subject has been copiously reviewed as "Atypical Face Pain" by McElin and Horton,[1] and Glaser,[2, 3, 4] to whose papers and bibliographies one is referred. These authors have in the main dealt with the pathways by which pain is referred, and have attempted to treat the pain by an attack on the pathway, while Kelly and Langheinz [5] appear to have made a step in attacking the cause of the pain, though their method seems quite complicated.

The following cases are presented:

Case 1. A 28 year old female dental assistant was seen because she had become alarmed by very severe pain in the right zygomatic region six weeks previously. The pain had not been relieved by analgesics. After roentgenogram the right upper wisdom tooth was claimed to be impacted and was removed. This relieved the pain. At the time of physical examination no abnormalities other than an absent lower right six year molar and a secondary anemia were noted. Roentgenograms of the sinuses and teeth revealed no roentgenologic abnormalities. She was advised to have a fixed sanitary bridge to replace the absent six year molar (which advice was not followed), and after the correction of the anemia was not seen for eight months. At this time she had a sudden return of her severe pain associated with persistent vomiting. The sinuses transilluminated well and there was no tenderness over the sinuses. It was apparent that the lower right 12 and 18 year molars had tilted mesially, so that the distal cusps were higher than the remainder of the respective separate teeth, also higher than the occlusal line, and in forward motion of the mandible these distal cusps exerted a cam action against the similar cusps of the upper molars. She stated that she did most of her chewing on the right side. The lower two right molars were ground so that the right side of the jaw occluded simultaneously with the left side of the jaw, and her pain has not reappeared.

Case 2. A 78 year old white female physician was scratched in the nasolabial fold by a cat. Within 48 hours the area showed an extensive, weeping, spreading, impetiginous lesion. Self-medication for several days was unavailing. A dermatologist was consulted, but no improvement occurred. Because of bleeding gums and purulent exudate at the gingival margins, she consulted one of us (W. L.), who noted recession of spongy, easily bleeding gums in the central areas, where malocclusion was forcing the closed lower incisors and cuspids against the uppers. These lower teeth were ground sufficiently to allow clearance on occlusion. The following day the face was much improved, and by the third day was completely healed. Except for gingival recession the gums returned to normal, and the bleeding and purulent exudate ceased with this relief of abusive stress.

Case 3. A 38 year old white female, the wife of a physician, saw her otolaryngologist for severe pain in the right ear. After careful study the otolaryngologist

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told her there was nothing abnormal within the scope of his specialty, but that she should see her dentist. Fixed sanitary bridges had been placed in the lower jaws to replace absent six and 12 year molars, and on examination the right bridge was found to have a high spot which struck the upper 12 year molar prematurely on occlusion. This high spot, about 1/1000 inch, was ground off, and the patient has had no recurrence of the pain in her ear for four years.

Case 4. A 35 year old physician had marked recession and periodic bleeding of the gums for some years. Massive doses of vitamins C and K had stopped the bleeding intermittently during medication, but had not permanently corrected either the bleeding, recession, or sponginess of the gums. He had seen several dentists as he moved around the country in pursuit of his training. At age 21 his lower left six year molar had been removed. When seen, the gap between the lower left fifth and seventh teeth had narrowed to 7 mm., and a gap had appeared between the lower left third and fourth teeth measuring 4 mm. The lower central incisors were crowded out of line, twisted, and overlapping. His teeth were extremely sensitive. At no time had he ever been advised to have the lower left six year molar replaced. Marked malocclusion was present in the lower left jaw because of depression by mesial movement of the molars and bicuspids.

A fixed sanitary bridge was inserted. The upper left and lower right six year molars were loose, had marked recession of the gums and alveolar processes (roentgenograms), and attempted correction by the procedure to be outlined allowed only further extrusion of these two molars. These were removed and fixed sanitary bridges were inserted. His occlusion was corrected and the pyorrhea and bleeding improved markedly, except in the area of the lower left second and third teeth, which were found to grind against his upper left central incisor when asleep. These three teeth were ground further to allow clearance (even when asleep) and improvement was noted. Pressure of the tongue against the lower central teeth, a habit acquired in blowing smoke rings, was causing considerable stress on these teeth, and further improvement in the condition of the gums was noted when the habit was broken. However, the gap between the lower left third and fourth teeth has increased, and there is further crowding and torsion of the lower left incisors; as they move and are subject to abnormal stress and strain, they are ground to allow clearance, and it is hoped that they will soon stop moving.

Case 5. A 30 year old white female was admitted to the hospital with severe cardiac decompensation, rheumatic heart disease, and marked valvular deformities. During convalescence she began to note annoying pain which, though momentary, was severe and stabbing, starting in the neck and radiating up into the face in the infraorbital regions. The teeth appeared in good condition except for a small cavity in the lower right six year molar. There did not appear to be any recession of the gums or the alveolar processes; roentgenograms of the teeth and sinuses were normal. Because of her general condition it was not deemed advisable to repair the six year molar at this time, and the pain was controlled ineffectively with salicylates. Shortly after returning home to continue her convalescence the gum around the upper left six year molar began to bleed on brushing, and she complained that it was sensitive. No caries could be found in this tooth and soon the gum began to recede. Because her heart condition was progressively deteriorating it was not felt advisable to do anything to the teeth except to continue the program of analgesics. However, the pain increased in severity, duration and frequency, and required codeine for relief. When codeine was no longer sufficient to control the pain without completely destroying her appetite and bowel habits, it was decided to remove the upper left six year molar as the simplest procedure in the home. This was done with relief of the abnormal stress and strain between the two left six year molars, and there was a cessation of the pain for the remaining seven months of her life.

Case 6. A 60 year old white female nurse had severe osteo-arthritis of the right hip as a late result of trauma as a young woman. This was becoming progressively more crippling. In February 1947 she developed a corneal opacity in her left eye. She was seen and treated locally by her ophthalmologist. From February to July 1947 she had a recurrence of corneal opacities in either eye on seven separate occasions, each recurrence becoming more severe and more resistant to treatment. In July, when she had a corneal opacity with iritis in the right eye, she was seen by an internist who noted the following oral condition:

The fifth left upper tooth had been removed the year previously because of crowding in the upper incisor region, and the upper left sixth, seventh, and eighth teeth had angled forward to close the gap. There was extreme recession of the gums of all upper molars. The lower molars had been replaced by a removable bridge which clasped on to both lower fifth teeth. The patient complained of some irritation of the gum below the left side of the removable bridge. There was marked recession of the gum of the lower left fifth tooth. The lower remaining teeth were bearing considerable weight and were badly worn. The gums bled easily and the teeth were quite loose.

It was advised that the bridge be removed and left out. Within 12 hours there was marked improvement in the iritis and the corneal opacity was definitely smaller. In 36 hours the opacity had disappeared.

Roentgenograms showed excessive alveolar destruction throughout, and a periapical abscess at the base of the lower left fifth tooth. With the exception of two teeth, there was so little bone holding the teeth that, at her age, it was advised she have all the teeth removed. This was done, at which time she had massive doses of penicillin prophylactically, and since then there has been no recurrence of corneal opacities or iritis. Incidentally, her osteo-arthritis is much less painful and considerably less crippling.

Case 7. A 25 year old white female housewife was seen for a complaint of pain in the right eye of three months' duration. Associated with this at times was pain which began at the vertex and spread down over the whole right side of the head and neck. The progressive intensification of symptoms was beginning to cause insomnia. Aspirin, which had been beneficial in the beginning, was losing its efficacy. She admitted to chewing solely on the right side of the jaw. On examination the gums were found to be in excellent condition, one-sixth of the right upper cuspid was worn off, the lower left bicuspids were displaced buccally and were not bearing much, if any, weight. The weight was borne mainly by the teeth on the right side.

The right bicuspids and molars were ground slightly, so that the two sides of the jaw were balanced to bear weight equally, and to occlude simultaneously. She was warned that she had a habit of grinding the right cuspids, and she was discovered to have a sliding lateral motion on the right cuspids when concentrating on problems. She corrected her grinding habit, pain in the right eye ceased completely, and in a few days the other symptoms disappeared. The cessation of abusive stress has obviated any need for further treatment in seven months.

Discussion

The procedure used in this method of treatment of pain and pyorrhea is very simple. Red carbon paper, coated on both sides, is applied between the teeth and the patient is asked to bite normally, i.e., as he would were he chewing meat. Any abnormally high spots will be colored red. These can then be removed by a small grindstone. Care must be exercised to check the whole mouth and to balance the two sides, so that they occlude simul-

taneously. Also, care must be exercised, if much grinding is necessary on the "grinding" teeth (the molars and bicuspids), to be sure that the "cutting" teeth (the incisors and cuspids) do not become "weight-bearing" teeth and subject to abnormal and excessive stress and strain for which they were not designed. When the "grinding" teeth, which are the normal "weight-bearing" teeth, are worn or ground excessively there is an increased closure of the temporomandibular joint, and the lower incisors are brought further forward and up, so that they will occlude against the posterior surfaces of the upper incisors. This in turn subjects them to "weight-bearing."

Occasionally one will note a very powerful cam action between opposing cusps, especially if there be any lateral motion of the jaw during occlusion, which can subject the involved teeth to excessive strain; often under these conditions there will be found excessively tender teeth. In like manner, excessive stress can be applied to teeth if they be struck continually in a plane other than the longitudinal axis of the tooth, e.g., when the tooth has angled over to fill in a gap following the removal of another tooth. This pressure is then maximally exerted at the weakest point of the tooth at the gum line. The root of the tooth is firmly imbedded, and the force is applied by leverage at the weak fulcrum (gingival margin). This in turn causes an abrasion and laceration at the gingival margin which is being continually traumatized. Teeth so exposed to continuous abusive stress can become exquisitely tender, so much so that the patient is sure that caries is present. The proof of sensitivity being caused in this way can be shown by four facts: (1) the frequent absence of any caries; (2) the extreme sensitivity of the tooth to the application of metal, metallic salts, or pressure above the enamel; (3) the extreme sensitivity of the tooth to any drilling, brushing, or sweets; and (4) probably the most conclusive proof, the disappearance of the sensitivity of the tooth and all portions thereof when the abusive stress has been removed.

Many mouths will be seen which are very dirty in the absence of proper dental hygiene, in which no pyorrhea is present. The reverse is equally true where the hygiene by the patient and attention by the dentist are scrupulously observed. The answer, we feel, lies in not traumatizing the abrasion and laceration. When an external injury interrupts the continuity of the integument, every effort is made to relieve it from every possible irritation or stress by complete immobilization. The same basic principle should be applied to the teeth and their supports; the teeth are not made of rubber, but when subjected to abusive stress will impart the stress to their supporting structures and incidentally irritate the nerve supply.

If physicians and dentists will pay attention to the little signs of spongy, bleeding and receded gums, purulent exudate and calcareous deposits at the gingival margins, malocclusion and absent teeth, they will often discover minor defects in the mouth which, with the application of good preventive medicine, may be corrected easily at the time. If allowed to progress they may become of major importance and lead to extensive dental repairs.

Moreover, they may be associated with unusual and often puzzling and distressing symptoms of pain, sensitive teeth, earache, temporomandibular crepitation and pain, pyorrhea, iritis, and other infection. In this connection we wonder if there might be a relation between abusive stress of the teeth and trigeminal neuralgia.

We are not attempting an elucidation of the pathways by which pain is referred from the teeth to various portions of the face and head in these bizarre cases. The reader is referred to the various texts on neuro-anatomy and neurophysiology. We feel that in at least some of the cases of face pain there is a definite relationship to the teeth, and that by very simple procedures this can be corrected. We do not feel that extensive procedures are indicated, nor do we think that it is necessary to treat the pathways by which pain is referred in order to treat the pain. We are offering a simple explanation for pyorrhea, some cases of face pain, and some unusual and distressing signs of infection and bizarre symptomatology in the region of the face, eyes, ears, and head. We realize that the heyday of pulling teeth as a panacea so discredited the possible relationship between teeth and "disease" (difficult ease) that today this idea is in discard. We ask that this relationship be kept in mind, observing, of course, its proper perspective, especially in those cases where all other possible causes seem to be excluded.

Conclusion

A simple method of diagnosis and treatment of pyorrhea and of some cases of atypical face pain and other bizarre symptomatology is presented.

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PERIARTERITIS NODOSA—POSSIBLE RELATION TO THE INCREASED USAGE OF SULFONAMIDES*

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PERIARTERITIS nodosa, formerly considered a rare clinical diagnosis, is now being recognized more frequently. The medical literature of recent years contains many references to this disease. The increase in the number of reports on the subject concomitant with the wide usage of sulfonamides has prompted us to review the records of Bellevue Hospital before and after the availability of sulfa therapy.

Although information regarding the history of drug ingestion in our cases of periarteritis nodosa is lacking, it is generally agreed that such knowledge is difficult to obtain because many patients often receive the drug unknowingly and also that the sulfonamides are being dispensed with great frequency.

There were only four cases diagnosed ante mortem from 1916 to 1937, but from 1938 to 1946 there were 14 cases of periarteritis nodosa detected clinically and proved either by biopsy or necropsy. The latter cases appear below in table 1.

There were nine males and five females whose ages varied from 17 to 63. Eight patients gave a history of bronchial asthma in the past, an incidence of 57 per cent. An eosinophilia of over 10 per cent, ranging from 12 per cent to 41 per cent was present in 43 per cent of the cases. Three patients were discharged as improved, six died and five were unimproved.

The protean manifestations of this disease have frequently baffled the internist. Meyer's original triad of symptoms, i.e., chlorotic marasmus, polyneuritis and polymyositis, and abdominal symptoms, became a tetrad after Brinkman added nephritis to this syndrome. Subsequently additional features were observed so that at present the list of characteristics of this disease has grown. Solomon, Kasich and Kiven [1] separated the clinical and laboratory findings into four convenient groups. First, there are those occurring from the inflammatory process, such as fever, leukocytosis, general malaise, loss of weight, rapid sedimentation rate, anemia, and in general the picture of sepsis of unknown origin. Second, the group of symptoms arising from the involvement of the arteries of particular organs, such as the heart, nervous system, gastrointestinal system and kidneys. Third, the allergic manifestations as evidenced by eosinophilia in the peripheral blood and in the involved arteries histologically as well as the frequent association

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TABLE I

Name	Age	Sex	History of Bronchial Asthma	Biopsy	Autopsy	Eosinophiles	Precipitin Test	X-ray Evidence of Osteoporosis	Outcome
E. K.	42	M	Yes	Positive	0	1–15	Not done	Not done	Improved
J. F.	54	M	No	Positive	0	3–7	Pos. in 1:1280	Yes	Improved
R. A.	39	F	Yes	Positive	Yes, pos. P.N.	16–18	Not done	No	Died
A. K.	63	M	Yes	Taken from gall-bladder	0	1–3	Not done	No	Discharged Unimproved
F. W.	59	M	Yes	Positive	0	4	Pos. in 1:1280	Yes	Discharged Unimproved
D. B.	47	F	Yes	Positive	0	27–49	Pos. in 1:1280	Positive	Died
W. T.	17	M	No	Positive	0	1–5	Not done	Not done	Improved
W. B.	52	M	No	Positive	Yes, pos. P.N.	1–7	Not done	Negative	Died
S. D.	29	F	No	Not done	Yes, pos. P.N.	0	Not done	Not done	Died
L. H.	45	F	No	Not done	Yes, pos. P.N.	0	Not done	Not done	Died
B. O.	52	F	Yes	Positive	0	12	Not done	Negative x-rays	Discharged Unimproved
H. S.	34	M	Yes	Positive	0	35	Negative	Positive x-rays	Discharged Unimproved
J. G.	46	M	No	Positive	Yes, pos. P.N.	0	Not done	Negative	Died
E. B.	37	M	Yes	Positive	0	15–41	Negative	X-rays not done	Discharged Unimproved

TABLE II

Clinical Findings	Laboratory Findings
1. History of bronchial asthma	1. Eosinophilia
2. Cachexia	2. Leukocytosis
3. Polyneuritis and polymyositis	3. Anemia
4. Abdominal symptoms, i.e. (diarrhea, cramps, vomiting)	4. Elevated sedimentation rate
5. Fever	5. Positive precipitin test for trichinosis in a dilution of 1:1280
6. Vascular changes (as seen in eyegrounds)	6. Roentgen evidence of patchy osteoporosis
7. Nephritis and hypertension	7. Positive muscle or skin biopsy
8. Skin manifestations (urticaria, erythema, nodules)	
9. Arthralgia and arthritis	

of asthma; and fourth, palpable arterial nodules and positive muscle or skin biopsy.

Table 2 enumerates the salient features that were recorded in our cases.

It is important to remember that not all the above mentioned criteria must be present in any one case to warrant a clinical consideration of the diagnosis of periarteritis nodosa. However, only a positive biopsy or necropsy can be considered conclusive.

Two features that have not received sufficient notice are worth em-

phasizing. A positive precipitin test for trichinosis in a dilution of over 1:1000 was found in three of our 14 cases. This is significant inasmuch as the test was performed in only five cases. Patchy osteoporosis, as evidenced by roentgen-ray was present in four of our nine patients, which fact can be explained by changes in the vessels supplying the bones.

The pathologic picture of this disease has a characteristic pattern with which most authors agree. According to Arkin,[2] the lesions may be divided into four stages: a degenerative stage, an acute inflammatory stage, a stage of granulation, and a so-called healed stage. The disease involves the smaller and middle sized arteries and arterioles either in segments or in their entirety. The fundamental pathologic change is an inflammatory lesion of the vessel wall with necrosis, fibrinoid alteration and hyalinization of the media of the affected arteries, together with perivascular infiltration with mononuclear and polymorphonuclear leukocytes which are often eosinophiles. Injury of the intima leads to thrombosis and medial injury and dilatation result in the formation of aneurysms, which may rupture and produce fatal hemorrhage. Organization of the thrombosed aneurysms may give rise to firm periarterial nodules.

Many theories have been advanced concerning the etiology of periarteritis nodosa. The very early writers mention syphilis as a possible cause, but with the development of the Wassermann reaction, the idea was no longer tenable. Mechanical causes and parasitic infections were considered as responsible agents but were never proved. Many bacteria and a filtrable virus have been accused but not definitely isolated. Neurologic and toxic factors have had their proponents but with very little support. Hypersensitivity as an etiologic factor in the production of periarteritis was first suggested by Gruber in 1923.[3] Since then many other observers have subscribed to this theory, and the recent work of Rich[4] and Rich and Gregory[5] has added great impetus to this concept. Rich[4] described vascular lesions characteristic of periarteritis nodosa in the viscera of five patients who shortly before death had hypersensitive reactions following therapeutic injections of foreign serum and sulfonamides, and in one patient who had received sulfathiazole prophylactically to prevent aspiration pneumonia. The possibility that the infection for which these patients were treated might be implicated was negated by the experimental reproduction of similar lesions in rabbits by the injection of horse serum and horse serum plus sulfadiazine. These observations caused Rich to advance the idea that periarteritis nodosa may well be a manifestation of hypersensitivity.

Discussion

We noted the predominance of males over females in a ratio of almost two to one, a fact which is generally well recognized. The frequent association of bronchial asthma with periarteritis nodosa has been observed by many authors. Rackeman and Greene[6] reported an incidence of 12 per cent,

and Wilson and Alexander [7] found a somewhat higher figure, 18 per cent. The 57 per cent that we noted, although considerably higher, can be explained by our relatively small series. The blood eosinophilia of 43 per cent is within the expected range noted by previous writers.

Our series of 14 cases, although not large, is particularly significant in a condition as uncommon as periarteritis nodosa. The significant rise in the number of cases diagnosed after the introduction of sulfonamides suggests the possibility that the drug may play a rôle in the etiology of this disease.

We agree that increased interest in periarteritis nodosa may have been a factor in sharpened diagnostic acumen; nevertheless, the relation of the wider usage of sulfonamides to the figures presented cannot be questioned. In analyzing the necropsy material at Johns Hopkins Hospital, Rich [8] noted that during the years from 1916 to 1935 the characteristic picture of periarteritis nodosa was found in only one or two cases per five year period. In a similar number of autopsies performed from 1936 to 1940 there were 15 cases of periarteritis nodosa and in the five year period from 1941 to 1946 there were 23 cases.

There is sufficient accumulated experimental and clinical evidence to indicate that sulfonamides can produce hypersensitivity. Schönholzer [9] and David [10] demonstrated that sulfa drugs can attach themselves to plasma protein and that the complex so formed can behave as an antigen. Wedum [11] was able to produce anaphylactic shock and positive intradermal reactions by conjugating sulfonamide compounds to human and rabbit serum. Gerber and Gross [12] produced anaphylaxis and the Schwartzman phenomenon in guinea pigs and rabbits with conjugated sulfa compounds. Schaeffer, Lentz and McGuire [13] in 1943, reported a positive Prausnitz-Kustner reaction to sulfathiazole with serum and blister fluid from persons reacting to the drug a second time. Leftwich [14] in 1944 clearly demonstrated that specific cutaneous reactions can occur by employing the serum of patients treated with sulfonamides who gave no reaction, and inoculating it into those who reacted with a typical hypersensitive pattern.

Shortly after sulfonamides were employed clinically, Hageman and Blake [15] in 1937, reported the serum-sickness like reactions of a group of patients who were treated with sulfanilamide. Goodman and Levy [16] were among the first to suggest that the rash appearing after treatment with sulfanilamide was the result of hypersensitivity even though the skin tests in their two cases were negative. Thereafter many similar reactions were noted and reported.

Many observers have described vascular changes resembling periarteritis nodosa following the use of sulfonamides. Lederer and Rosenblatt [17] found necrosis and infiltration of inflammatory cells in the viscera of four patients who died from sulfathiazole intoxication. The histologic picture that Rich [4] noticed in his five cases who received serum and sulfonamides consisted of

fibrinoid necrosis with perivascular infiltration of mononuclear cells and eosinophiles, a picture not unlike that seen in periarteritis nodosa. Although Clark and Kaplan [18] demonstrated a similar arterial lesion in patients who had serum-sickness shortly before death, Rich also observed fibrinoid necrosis at necropsy in two patients who received sulfathiazole without serum. This led Rich to reason that sensitization to sulfonamides does occur and that under such circumstances periarteritis-like lesions may be caused by the administration of the drug.

Rosenak and Maschmeyer [19] reported a case of periarteritis nodosa in a patient who received sulfadiazine and died. More recently, Goodman [20] described a case of periarteritis nodosa proved by biopsy, in whom the apparent cause was sulfadiazine sensitization. The patient recovered following a severe prolonged anaphylactic reaction produced by the unwitting administration of the drug at the height of the patient's illness. Black-Schaeffer [21] in describing five cases of anaphylactic death following therapeutic use of sulfonamides noted arterial lesions which varied from simple edema to frank necrosis. Although the necrotizing vascularitis mentioned was not quantitatively comparable to the typical lesion of periarteritis nodosa, the author felt that the basic pattern was so similar that it suggested a difference of intensity and duration of action rather than the quality of the irritant.

Inasmuch as sulfonamides can produce hypersensitive reactions and a vascular necrosis resembling periarteritis nodosa has been described following its administration, it is reasonable to assume that the increased number of cases of periarteritis nodosa reported clinically at our institution since the introduction of this chemotherapeutic agent may be explained by a hypersensitivity to sulfa compounds.

Summary

1. A review of the records of Bellevue Hospital during the years from 1916 to 1937, before the introduction of sulfa therapy, revealed only four cases of periarteritis nodosa diagnosed ante mortem.

2. After the wider usage of sulfonamides, from 1938 to 1946, there were 14 cases recognized clinically and proved either by biopsy or necropsy.

3. A history of bronchial asthma was present in 57 per cent of the cases and eosinophilia of over 10 per cent occurred in 43 per cent of the 14 patients.

4. The pathology and various etiologic factors of periarteritis are discussed.

5. Evidence that hypersensitivity to sulfonamides does exist is presented.

6. The vascular lesions resembling periarteritis nodosa following sulfonamide administration and the increased incidence of periarteritis since the introduction of the drug are offered as evidence that a possible relation exists between sulfonamides and the disease, periarteritis nodosa.

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OBSTRUCTION OF THE SUPERIOR VENA CAVA: A REVIEW OF THE LITERATURE AND REPORT OF TWO PERSONAL CASES *

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Introduction

The superior vena caval syndrome is due to obstruction of the superior vena cava, bilateral innominate vein obstruction or arteriovenous fistula between the ascending aorta and superior vena cava. This presentation is limited to a discussion of obstruction of the superior vena cava, either partial or complete. It does not include bilateral innominate vein obstruction or arteriovenous communication between the superior vena cava and ascending aorta, unless these conditions are found coincidentally with superior vena caval obstruction. Perfection of technic of angiography, phlebography, venous pressure, and circulation time has stimulated renewed interest in this syndrome. The clinical picture results from increased venous pressure in that part of the body which normally has its venous return to the superior vena cava, delayed circulation time, collateral diversion of the blood stream, and the associated manifestations of the primary pathologic process causing the obstruction.

Historical Data

There is considerable confusion in the literature in regard to whom credit should be given for priority of publication on this subject. Both Fischer [150] and Ehrlich, Ballon, and Graham [42] state that Corvisart, in 1806, was the first to report marked narrowing of the superior vena cava and Marjolin, in 1819, was the first to report complete obliteration of this vessel. According to Ochsner and Dixon,[89] Zambellini (1900) states that the first two reported cases of superior vena caval thrombosis were by Bartolino and Hunter. In referring to the original publication of Zambellini,[160] we find that he actually gives priority of publication to Bartolino; however, our investigation indicates that Bartolino probably did not publish an authentic case. There are numerous publications by authors named Bartolino or Bartholinus during the 17th and 18th centuries and we find in the writings of Thomas Bartholinus,[148] 1740, reference to a case of death by suffocation in which a post mortem was done by Riolanus, who described a "small bit of flesh with shapeless fat in the orifice of the vena cava." The reference is vague and the author does not state whether the fleshy material was in the inferior or the superior vena cava.

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William Hunter,[151] in "Medical Observations and Inquiries," 1757, reports a case of superior vena caval obstruction from aortic aneurysm in a man who died October 29, 1752. An autopsy was done and drawings were made. On page 333 of his report, in the explanation of the various parts of the first drawing, is the following statement: "L, the vena cava superior; and M, the common trunk of the left subclavian and jugular vein; both so much compressed by the dilated artery as hardly to have anything left of their natural capacity and appearance." This report by Hunter, apparently, is the first authentic description of a case of obstruction of the superior vena cava. Consequently, the literature dates back 190 years and antedates the reports of Corvisart and Marjolin by approximately one-half century.

Following the report by William Hunter,[151] 1752, and later those of Corvisart, 1806, and Marjolin, 1819, came the inaugural dissertations of Deckart, 1823, Weissbrod, 1831, Poschel, 1903, and Fischer,[150] 1904. Fischer's contribution provided the most comprehensive review of the subject up to that time.

Review of the Literature

Fischer, 1904, collected 252 cases from the literature. In 226 of these, autopsy had been performed. This, according to the author, represented the cases published up to that time "so far as they were available to him." Rauth,[104] however, stated that Hume, in 1903, at the instigation of Osler, reported 29 cases, 12 of which were not included by Fischer. Rauth,[104] 1911, collected nine additional cases from the literature after 1904, all verified by autopsy except one. Dana,[36] 1922, collected 23 more after 1911, and Ehrlich, Ballon, and Graham,[42] 1934, collected eight after 1922. From 1934 to January, 1946, inclusive, we have collected 111 cases, 56 of these proved by autopsy.

We have not searched for reported cases prior to the dissertation by Fischer, 1904, but in the above summaries of the literature from 1904 to 1934 many case reports have been omitted. We have divided the literature arbitrarily into four periods since Fischer's contribution represented by the publications of Rauth,[104] 1904 to 1910, inclusive; Dana,[36] 1911 to 1921, inclusive; Ehrlich, Ballon, and Graham,[42] 1922 to 1933, inclusive; and the portion of our review covering the period 1934 to January, 1946, inclusive. It is assumed that the various authors could not have reviewed the cases published in the year of their own publication with the exception of the cases which they contributed themselves. During the period 1904 to 1933, there are 100 cases in the literature not reported in the summaries of Rauth; Dana; and Ehrlich, Ballon, and Graham; 73 of them proved by autopsy (table 1).

Rauth, in reporting his nine collected cases, did not provide a complete bibliography but mentioned the following authors as source of his material: Osler, Leyden and Westenhoffer, Weinberger, Vigoureux and Collet,

Poeschel, and Revilloid. From this group, we have included only the case of Leyden and Westenhoffer [74] in our series for review. Satisfactory data concerning the cases by Weinberger, and Revilloid could not be obtained. The publications by Osler and Poeschel were in 1903; our review begins with 1904. The case of Vigoureux and Collet apparently was reported in 1905 but had previously been reported by Comby before the Societé Medicale

TABLE I

Case Reports in Literature to 1946

Date	Source		No. of Cases	Bibliographic References		Remarks
				Verified Cases*	Unverified Cases*	
Prior to 1904	Hume, 1903		12			Included for completeness
	Fischer, 1904		252			
1904 to 1910	Rauth	Literature	9			
		Personal	4			
	Cases in literature not collected by Rauth		30	2, 13, 26, 32, 38, 41, 50, 56, 63, 65, 66, 69, 73, 78, 91, 105, 106, 108, 119	10, 40, 41, 94, 118, 121, 127	23 of these cases were verified by autopsy
1911 to 1921	Dana	Literature	23	5, 6, 8, 37, 44, 52, 53, 57, 59, 70, 92, 93, 122, 123, 128, 133, 136, 137, 144, 145	1, 22, 33, 51, 54, 57, 58, 61, 75, 76, 97, 124, 126, 131, 137	Dana's bibliography is incomplete. It is not possible to determine what cases he reviewed. Of the 43 cases in the literature, 25 were verified by autopsy
		Personal	1			
	Cases in literature not collected by Dana		20			
1922 to 1933	Ehrlich, Ballon and Graham	Literature	8	15, 19, 21, 47, 67, 110, 132, 138		Berblinger [15] reported 2 cases; Ehrlich et al. apparently took only one. Of the 50 cases, not reviewed by Ehrlich et al., 25 were verified by autopsy
		Personal	2			
	Cases in literature not collected by Ehrlich, Ballon and Graham		50	15, 27, 34, 62, 72, 84, 86, 87, 88, 100, 113, 114, 116, 117, 120, 129, 140, 141, 142, 147	17, 28, 29, 30, 35, 49, 77, 90, 95, 98, 103, 109, 111, 114, 130, 139, 141, 142, 143, 146	
1934 to Jan. 1946 incl.	McIntire and Sykes	Personal	2			
		Literature	111	4, 9, 11, 12, 14, 16, 18, 20, 25, 31, 39, 43, 46, 55, 60, 64, 71, 80, 81, 82, 83, 85, 89, 96, 99, 101, 102, 107, 112, 115, 134, 135	3, 7, 23, 24, 45, 48, 60, 64, 68, 79, 96, 99, 107, 125	56 of these cases were autopsied
	Total		524			

* Verified cases—autopsy or surgery done.
Unverified cases—autopsy or surgery not done.

des Hôpitaux de Paris, January 8, 1892, while the case was under Comby's care. We are not including our two personal cases since this series represents a collection from the literature exclusively. There remains in the total series (table 1) 250 cases from 1904 to January 1946, inclusive, after excluding eight cases by Rauth and our two personal cases. This is an interesting total to compare with Fischer's 252.

Of these 250 cases, the etiology of the obstruction in 145 was proved

by autopsy or surgery. We considered unquestionable proof of etiology dependent upon pathological finding from autopsy or surgery and adhered to this more rigid ruling throughout. The remaining 105 cases were clinical diagnoses, and this group includes only those cases in which there was good evidence in the publications that the patient actually had superior vena caval obstruction.

Doubtless many cases have been missed in the larger series. The report of Hinshaw and Rutledge [60] is a study of 31 cases representing various types of mediastinal obstruction. On the basis of their clinical reports there is sufficient evidence to support the diagnosis of superior vena caval obstruction in only 12 cases. Only four of 50 cases by Pilcher and Overholt [96] are accepted. There are not sufficient diagnostic data available to justify including any of the 30 cases reported by Serra [158, 159] on various types of venous pressure disturbances in mediastinal syndromes. For the same reason, none of 60 cases by Keefer [153] on the subject of acute and chronic mediastinitis are included. None of the 52 cases reported by Hussey [152] are accepted. However, 14 of these had high venous pressure in both arms and it is assumed that they were included in the report of 35 cases by Hussey, Katz, and Yater [64] which are included in our collection.

Incidence

In regard to the incidence of the syndrome under consideration, varying opinions are expressed in the literature. Ochsner and Dixon [89] state that "obstructions to the superior vena cava whether partial or complete are rare clinical and pathological entities." Forster [48] states that varying degrees of superior vena caval obstruction occur not uncommonly. We agree with the latter opinion.

It is our feeling that superior vena caval obstruction occurs much more frequently than is generally suspected. Common lesions such as aortic aneurysms, mediastinal malignancies, and chronic inflammatory diseases are responsible for the caval obstruction in a substantial majority of reported cases (table 4). Many cases of superior vena caval obstruction in the literature are doubtless hidden because of being reported as cases of the primary pathology, such as aortic aneurysm, mediastinal lymphoma, etc. Reports of large series of superior mediastinal venous obstruction of various types, such as those of Pilcher and Overholt,[96] Hinshaw and Rutledge,[60] and Serra [158, 159] give additional indication that the disease is not uncommon. It is significant that one group of observers who were alert to this condition, Hussey, Katz, and Yater,[64] should at one time report a total of 35 cases of superior vena caval obstruction, representing nearly 7 per cent of the largest total reported in the world's literature to date, namely our figure of 524 (table 1). The frequency of space occupying lesions of the superior mediastinum, the anatomical relations of the superior vena cava, the easy compressibility of this vessel, and the increasing number of case reports in the

literature (table 1), constitute in our opinion, very suggestive evidence that the syndrome is not uncommon.

Anatomical and Physiological Considerations

The following quotation from Hinshaw and Rutledge [60] is apropos: "The superior mediastinum is the great transportation center of the body. Through it passes all food on its way to the gastrointestinal tract, all air which enters and leaves the lungs, all lymph in the thoracic ducts, all blood which leaves the heart and which returns to it from the superior half of the body. It is surprising that obstructive symptoms do not develop more frequently than they do in this crowded region. It is more surprising still when the frequency with which the numerous mediastinal lymph nodes are involved in tumefactive processes due to inflammatory, tuberculous, and neoplastic lesions is recalled.

"The anterior and posterior boundaries of the superior mediastinum are firm and unyielding parts of the thoracic wall. The lateral boundaries are elastic, being separated from the spongy lungs by nothing more than the pliable pleural layers. Space occupying lesions can thus expand laterally.

"The trachea is well protected by its cartilaginous rings. Although frequently displaced, it is rarely collapsed by extrinsic pressure sufficient to produce obstructive symptoms. The esophagus lies in a somewhat protected region and its elasticity and power of independent motility makes serious functional impairment from extrinsic pressure rather uncommon. The great arterial trunks not only have firm walls, but the contained blood is under pressure sufficient to prevent interruption of the flow by an external force of reasonable intensity.

"The large mediastinal veins on the other hand are thin walled and the blood flowing through them is under very low pressure. Furthermore, these veins are anteriorly situated nearer the unyielding bony thoracic cage, against which they may be compressed by expanding mediastinal lesions. These veins drain blood from the upper half of the body only; from the upper extremities, the head, neck, and thoracic wall. Obstruction to flow of blood in these important channels will produce localized symptoms and signs pathognomonic of a mediastinal lesion. Since these vessels are readily compressed, such manifestations may be early indications (sometimes even initial symptoms) of serious mediastinal disease."

The ascending aorta lies in an anteromedial position to the superior vena cava and is immediately adjacent to it in most of its course (figure 1). Anatomically it seems most unlikely that a large aneurysm of this part of the aorta would fail to compress the superior vena cava to at least a moderate degree. The trachea and right bronchus hold a posterior and close relationship to the vena cava; direct extension to the vein by malignancy involving the anterior part of these structures could conceivably occur without much difficulty.

The importance of the relationship of certain mediastinal lymph nodes to the superior vena cava has not been sufficiently stressed in medical literature dealing with obstruction of this vessel. Two important chains of lymph nodes are intimately associated with the vessel: the right anterior mediastinal and the right latero-tracheal chains (Rouvière [157]). The former lies along the anterior surface of the superior vena cava and the right innominate vein and consists of two to five nodes. The latter lies on the posterior aspect of the same vein and consists of three to six nodes, the

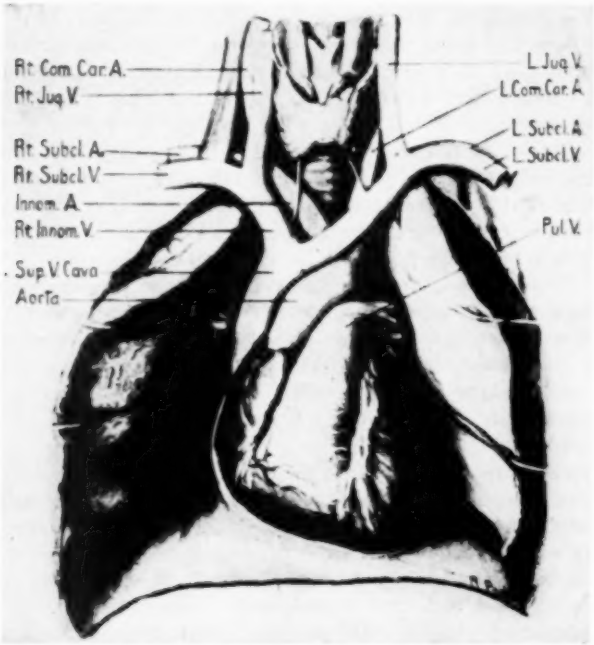

FIG. 1. Anterior view of mediastinal structures, showing the relationship of superior vena cava and ascending aorta. (Figure taken from Hussey.[152])

largest and most inferior of which lies on the superior surface of the arch of the vena azygos (figure 2). In addition, the right bronchial nodes and some of the nodes of the tracheal bifurcation are in fairly close association with the lower portion of the vena cava; both of these groups of nodes in turn drain into the right latero-tracheal chain. This chain (right latero-tracheal) receives most or all of the lymph drainage from the right lung, the lower trachea and proximal bronchi, the thoracic esophagus, and the lower portion of the left lung (figure 3).

The right anterior mediastinal lymphatic path receives some efferent vessels from the diaphragm, the diaphragmatic and mediastinal pleura, the heart, the pericardium, the right lung, and the thymus.

From the above, it is obvious that most of the structures of the right thoracic cavity, mediastinum, and part of the structures of the left thoracic

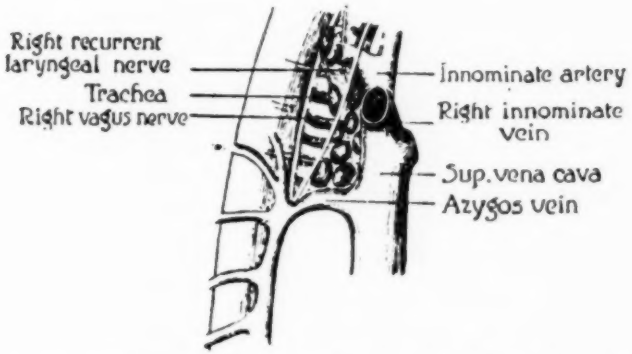

FIG. 2. The right latero-tracheal group of lymph nodes showing relationship between the nodes and the superior vena cava. Nodes are seen in the triangle formed by the azygos arch, the right vagus nerve, and the superior vena cava. (Figure by Sukiennikow, taken from Lerche.[154])

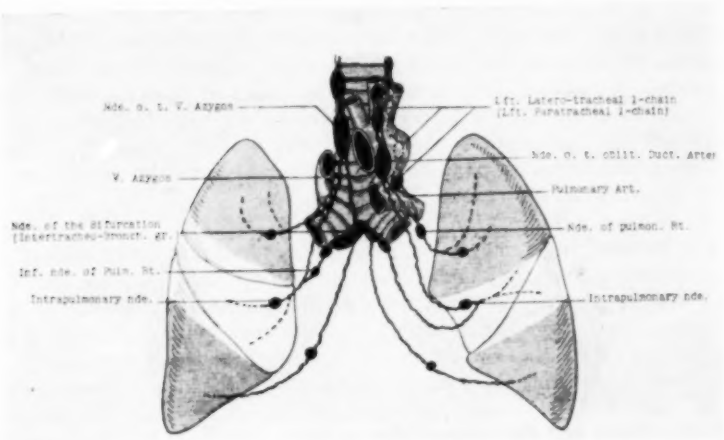

FIG. 3. Schematic representation of the pulmonary lymphatic drainage indicating the great area of pulmonary tissue drained by the right laterotracheal chain (one of the component nodes of this chain is the node of the vena azygos, labeled in this schema). (Figure taken from Rouvière.[157])

cavity, drain into either or both the right anterior mediastinal and the right laterotracheal chains (figure 3). The frequency of neoplastic and inflammatory disease in this part of the body serves as a constant threat to these lymph nodes with possible obstruction, partial or complete, of the superior vena cava from extrinsic pressure or invasion.

Collateral Circulation

Collateral diversion of the obstructed venous stream results in one of the characteristic features of the clinical picture—dilatation of certain subcutaneous veins. The efficiency of the collateral circulation is a factor in determining the prognosis and the degree of invalidism associated with the obstruction. Emphasis should be placed therefore upon the collateral routes available to the body. A composite, schematic diagram has been prepared to aid in the understanding of these routes and their mutual relationships (figure 4).

The superior vena caval system possesses four tributaries which carry the main burden of shunting the blood of this system toward the heart around an obstruction. Although none of these tributaries alone affords a direct connection between the superior vena caval system and the heart or inferior vena cava, the name of the tributary primarily involved in a particular route of collateral circulation will be used here to designate the route. Thus the terms internal mammary, vertebral, azygos, and lateral thoracic routes will be used below. All four routes are interconnected and all four are probably concerned in the collateral circulation regardless of whether the obstruction is above, below or involves the vena azygos orifice in the superior vena cava. The level of the obstruction with reference to the azygos orifice will indicate, however, which of the routes will predominate in the collateral flow. It should be realized that the four routes to be discussed do not constitute the total number of collateral pathways available to the body but merely those considered most important. The experimental work of Carlson [149] has been of considerable value in clarifying the subject of collateral circulation in superior vena caval obstruction.

1. Internal Mammary Route (heavy stipple—figure 4.): This route consists of the internal mammary vein, the superior and inferior epigastric, the musculophrenic veins, all the intercostal veins (except those of the first right and upper three or four left intercostal spaces), the anterior and posterior superficial veins of the thorax, the perforating branches of the internal mammary vein, and the medial mammary and posterior rami of the intercostal veins. Into this route is drained part of the blood of the vertebral route. Blood of the internal mammary pathway is ultimately drained into the vena azygos and the external iliac veins.

2. Vertebral Route (dark shade—figure 4): This route is composed of the vertebral and intervertebral veins, and the vertebral plexus (internal and external); it carries blood from the innominate veins and the dural

sinuses to the intercostal, lumbar, and sacral veins. Thus it drains partly into the internal mammary route and partly into the azygos route. Carlson[149] found this vertebral pathway to be an important one, particularly when the obstruction involved the vena azygos.

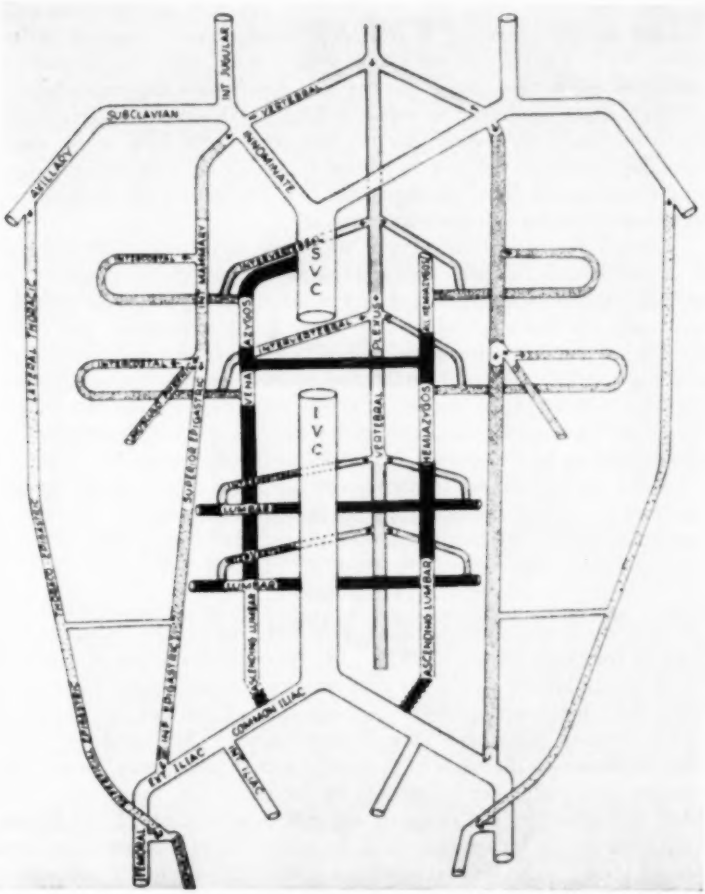

FIG. 4. Composite, schematic representation of the four principal collateral systems involved in superior vena caval obstruction.

3. Azygos Route (black color—figure 4): This route includes the vena azygos, hemiazygos, accessory azygos, ascending lumbar, and lumbar veins. Thus it affords communication between the superior and inferior venae cavae and receives part of the blood from the internal mammary and vertebral

routes. Its importance and the direction of the blood flow in it vary with the level of the obstruction. When the obstruction is above the azygos orifice the direction of blood flow is normal (toward the superior vena cava) and the vena azygos much dilated, forming an extremely important channel in returning blood to the heart (Carlson). When the obstruction involves the azygos orifice the blood flow is apparently reversed and the vena azygos diminished in size, forming a relatively unimportant collateral pathway (Carlson [149]). The part played by the azygos route when the obstruction is placed below the azygos orifice has not been determined experimentally; the two dogs Carlson subjected to superior vena caval ligation in this location failed to survive long enough for the collateral circulation to be studied. Presumably, however, the flow is reversed in this case, and theoretically the azygos route should form an important link connecting the superior vena caval system with the inferior vena cava.

4. Lateral Thoracic Route (light stippling—figure 4): This route consists of the lateral thoracic, thoraco-epigastric, superficial epigastric, and superficial circumflex iliac veins, their contained blood being poured into the femoral vein via the long saphenous vein. Being superficial, the veins of this route are readily seen when in a dilated state and are, therefore, of clinical importance. When the dilatation results from an obstructed superior vena cava the direction of blood flow is downward. Between this collateral pathway and the internal mammary route there exist communications which Carlson found to be extensively developed in the dog when the obstruction involved the azygos orifice. Only in obstructions at this level did the above author find the lateral thoracic route to be well developed; it was relatively unimportant where the obstruction was located above the azygos orifice.

Etiology

As indicated, our study is based on a series of 250 published cases appearing in the literature since 1904. In 166 of these the sex is given, 79.5 per cent being males and 20.5 per cent females. In Fischer's [150] series, 71.3 per cent were males and 28.6 per cent females. Thirty of the 35 cases reported by Hussey, Katz, and Yater [64] were males. These authors [64] explain the sex incidence on the basis of preponderance of aneurysms, bronchogenic carcinoma, and malignant lymphoma in the male.

Age was given in 164 cases in our collection and in 220 of Fischer's. We have shown the incidence in each decade of life in both series, as well as combined totals. The highest incidence is from age 30 to 60, probably corresponding to the age incidence of the common etiological factors, more particularly neoplasms and late syphilis, including aortic aneurysms (table 2).

We have not included, in our series, cases of mediastinal emphysema and pericardial obliteration as etiologic factors. For the sake of simplicity we have included, under the heading malignant lymphoma, cases listed in the

literature as lymphoma, lymphocytoma, lympho-adenoma, lymphosarcoma, lymphoblastoma, malignant lymphogranuloma, and Hodgkin's disease.

There is an attempt in some of the case reports to differentiate between tuberculous lymphadenitis and mediastinitis. A similar attempt is made to differentiate between gummatous and non-gummatous syphilitic mediastinitis. The differentiation of these two types of tuberculosis, as well as the two types of syphilis, lends itself to considerable inaccuracy, particularly when it is made on the basis of case histories, and probably is largely of academic interest. Consequently, we have grouped our cases of tuberculous lymphadenitis and mediastinitis together into one heading of tuberculosis and our cases of gummatous and non-gummatous syphilitic lesions under one heading of syphilis (table 3, Group V, A and B).

TABLE II

Age Period	No. Cases 1904 to Jan. 1946, Inc.	No. Cases before 1904 (Fischer)	No. Cases—Both Series	Per Cent—Both Series
0–10	1	3	4	1.04
11–20	9	12	21	5.48
21–30	24	33	57	14.85
31–40	33	38	71	18.50
41–50	38	71	109	28.40
51–60	36	33	69	17.95
61–70	18	27	45	11.70
71–80	3	3	6	1.56
81–90	1	0	1	0.26
91–100	1	0	1	0.26
Totals	164	220	384	100.00%

In tabulating etiology and disease incidence in the authors' collected series, the general plan of Ehrlich, Ballon, and Graham [42] in classifying Fisher's [150] cases has been followed. Comparative figures of disease incidence for both series are provided as well as the combined total. Percentage figures for Fischer's series are taken from Ehrlich, Ballon, and Graham.[42] Bibliographic references are listed according to etiology and separated into verified and unverified groups (table 3).

It is apparent that malignant primary thoracic tumors, aneurysms, and chronic fibrous mediastinitis are responsible for the obstruction in 75 per cent to 80 per cent of the cases in both Fischer's and the authors' series (table 4). Primary thoracic tumors, benign and malignant, account for 35.9 per cent of the cases in the combined series. Approximately 93 per cent of these are malignant. Syphilis (mediastinitis and aortic aneurysm) accounts for 34.8 per cent of the cases in the authors' collected series. Approximately 69 per cent of these are aortic aneurysms. Fischer's series was not included in this group since the subject of syphilitic mediastinitis, in his report, is rather obscure.

TABLE III

Etiology of Superior Vena Caval Obstruction

Group	Etiological Factor	Bibliographical Reference		Authors' Series				Fisher's Series (1)	Combined Series 2)
		Verified Cases*	Unverified Cases*	V*	U*	Total	%		
I.	Propagating thrombi from periphery	38, 101	23, 97	2	2	4	1.6	4.0%	2.8%
II.	Localized phlebitis with thrombus formation	12, 14, 16, 20, 25, 31, 32, 44, 73, 83, 115, 116, 117, 134	61, 96, 125	16	3	19	7.6	1.5%	4.55%
III.	Tuberculous phlebitis			0	0	0	0	1.5%	.75%
IV.	Actinomycosis			0	0	0	0	.5%	.25%
V.	Traction or compression by scar tissue (chr. mediastinitis)			30	32	62	24.8	6.0%	15.4%
	X A. Tuberculous	18, 55, 60, 66, 73, 78, 88, 92, 119, 135, 140	17, 48, 54, 99, 114, 126, 131	11	8	19			
	X B. Syphilitic	13, 15, 34, 37, 44, 91, 110, 129	11, 22, 33, 40, 51, 54, 75, 76, 94, 95, 98, 99, 103, 146	12	15	27			
	X C. Unknown—"idiopathic"	43, 55, 89, 112, 132	45, 49, 60, 96, 142	7	9	16			
VI.	Obliteration of pericardium			0	0	0	0	.5%	.25%
VII.	Thoracic tumors								
	A. Primary thoracic tumors								
	1. Benign	56, 81	79	2	1	3	1.2	4.0%	2.6%
	2. Malignant			48	26	74	29.6	37.0%	33.3%
	X a. Lung and bronchi	6, 21, 36, 39, 46, 64, 67, 80, 82, 102, 104, 136, 137, 142	60, 64, 107	19	3	22			
	X b. Esophagus	136		1	0	1			
	X c. Thymus	2, 19, 47, 122, 133		5	0	5			

TABLE III—*Continued*

Group	Etiological Factor	Bibliographical Reference		Authors' Series				Fischer's Series (1)	Combined Series (2)
		Verified Cases*	Unverified Cases*	V*	U*	Total	%		
	X d. Malignant lymphoma	8, 42, 53, 64, 72, 96, 99, 147	3, 24, 35, 45, 60, 96, 99, 107, 137, 141, 142	12	17	29			
	X e. Chorionepithelioma	46		1	0	1			
	X f. Leukemia	52, 64		3	0	3			
	X g. Sarcoma	57, 60, 107, 137, 142	57, 130	5	2	7			
	X h. Unclassified	72, 114	1, 121, 141, 142	2	4	6			
	3. Unclassified	106, 113	7, 57, 64, 114, 127	2	10	12	4.8		2.4%
	B. Extrathoracic malignant tumors								
	1. Metastasis to thoracic organs	42, 64, 142	3	4	1	5	2.0	4.25%	3.125%
	2. Tumors breaking into tributary of S.V.C. and growing down into it			0	0	0	0	4.25%	2.125%
	3. Metastasis to vein wall itself			0	0	0	0	.5%	.25%
	C. Aortic aneurysm			39	21	60	24.0	36.0%	30.0%
	1. Aneurysm alone	9, 41, 50, 62, 64, 84, 100, 102, 104, 123, 128, 129, 138, 141, 144	3, 28, 29, 30, 41, 45, 64, 90, 109, 111, 124, 139	18	21	39			
	X 2. Aneurysm with perforation into S.V.C.	4, 5, 10, 26, 27, 59, 63, 64, 65, 66, 69, 70, 71, 74, 85, 93, 105, 108, 120, 145		21	0	21			
VIII.	X Etiology not stated	86, 87	58, 64, 68, 77, 118, 143	2	9	11	4.4	0	2.2%
			Total	145	105	250	100	100%	100%

* "V"—Verified cases—autopsy or surgery done.
"U"—Unverified cases—autopsy or surgery not done.

(1) Fischer's series—252 cases.
(2) Combined series—502 cases.

X Additions to Ehrlich, Ballon and Graham's table.

There are 74 malignant primary thoracic tumors in our collection, 48 of which were proved by autopsy (table 5). Twenty-five per cent of these verified cases are due to malignant lymphomas of various types; and approximately 40 per cent are due to malignancy of lung and bronchi, all reported as carcinomas except two, which are stated to be primary fibrosarcoma of the bronchi.[137, 142] Figures based on unverified cases are not reliable (table 5).

TABLE IV

Percentage Table—Major Etiologic Groups (See Table 3)

Etiological Group	Authors' Series			Fischer's Series	Combined Series (502 Cases)
	Total Series—Verified by Autopsy (145 Cases)	Total Series—Not Verified by Autopsy (105 Cases)	Total Series—Verified and Unverified (250 Cases)	252 Cases—226 with Autopsy	
Traction or compression by scar tissue (chronic mediastinitis)	20.7	30.5	24.8	6	15.4
Primary thoracic tumors —malignant	33.0	24.7	29.6	37	33.3
Aortic aneurysms	26.9	20.0	24.0	36	30.0
Total	80.6%	75.2%	78.4%	79%	78.7%

Aneurysms have been subdivided into aneurysms alone and aneurysms with perforation into the superior vena cava, or arteriovenous aneurysms. Hussey, Katz, and Yater,[64] in referring to previous reviews of Fischer,[150] Brown,[21] and Ehrlich, Ballon, and Graham,[42] state that the only etiological factor not included in the reviews above mentioned is communication between an aortic aneurysm and the superior vena cava. Our findings are at variance with those of Hussey, Katz, and Yater.[64] In referring to Fischer's publication, we find the report by Pepper and Griffith [155] in his bibliography and note that Fischer included at least 15 of Pepper and Griffith's 29 cases in his report. The case by Leyden and Westenhoffer,[74] reported by Rauth,[104] is one of arteriovenous aneurysm. Hussey, Katz, and Yater have two cases of aortic aneurysm with arteriovenous fistula in their publication. We have included case reports of this type in our collection provided there was stated to be a definite associated occlusion or constriction of the superior vena cava. There are 21 of these cases in our total, all of them proved by postmortem examination. The subject of arteriovenous aneurysm involving the aorta and superior vena cava has been admirably reviewed by Pepper and Griffith [155]; Shennan [120]; and Armstrong, Coggin, and Hendrickson.[4]

Nineteen cases of localized phlebitis with thrombus formation have been reported since 1904, 16 of them verified by autopsies. In regard to etiology, 11 were of unknown cause, three were associated with cardiac disease, three were caused by mediastinitis, one was associated with silicosis, and one was classified as tuberculous endophlebitis. Fischer has a group of tuberculous

endophlebitis cases, listed by Ehrlich, Ballon, and Graham as comprising 1.5 per cent of his series. However, it is our opinion that these cases should be placed in the group "Localized Phlebitis with Thrombus Formation." Consequently, our one case is placed in that category.

TABLE V

Percentage Table—Primary Thoracic Tumors, Malignant—(See Table 3)

Etiological Factor	Verified by Autopsy (48 Cases)	Not Verified by Autopsy (26 Cases)	Combined Groups—Verified and Unverified (74 Cases)
Malignancy of lungs and/or bronchi	39.60	11.5	29.70
Malignancy of esophagus	2.09	0	1.35
Malignancy of thymus	10.40	0	6.75
Malignant lymphoma	25.00	65.5	39.20
Chorionepithelioma	2.09	0	1.35
Leukemia	6.25	0	4.07
Sarcoma	10.40	7.7	9.45
Unclassified	4.17	15.3	8.13
Total	100%	100%	100%

The "Traction or Compression by Scar Tissue" group has been divided into three subheadings: tuberculosis, syphilis, and a group of unknown cause. This, we believe, follows the intent of Fischer who mentions tuberculosis and syphilis as causative agents as well as a group of cases known as "indurated mediastinopericarditis." Terminology is simplified and clarified by referring to this group as one of chronic fibrous mediastinitis of tuber-

TABLE VI

Percentage Table—Chronic Fibrous Mediastinitis Group (See Table 3)

Etiological Factor	Verified by Autopsy (30 Cases)	Not Verified by Autopsy (32 Cases)	Combined Series—Verified and Unverified (62 Cases)
Tuberculosis	36.7	25.0	30.7
Syphilis	40.0	47.0	43.5
Fibrous mediastinitis, "idiopathic"	23.3	28.0	25.8
Total	100%	100%	100%

culous, syphilitic or idiopathic origin. Since 1904 a total of 62 cases have been reported and the incidence of each of the etiologic factors is shown in table 6. Change in the incidence of these factors is represented in table 7 according to time intervals corresponding to the reports of Rauth; Dana, Ehrlich, Ballon, and Graham; and the interval which we are reporting. The spectacular drop in incidence of chronic syphilitic mediastinitis from 28.6 per cent down to 0.9 per cent speaks well for the improvement in modern

diagnostic technic and the efficacy of present antisyphilitic therapy. The gradual decline in the incidence of chronic tuberculous mediastinitis from 11.4 per cent to 5.4 per cent is not as spectacular, but nevertheless speaks well for the effectiveness of modern measures in the prevention and treatment of tuberculosis. Idiopathic, or non-specific, chronic fibrous mediastinitis has only recently been reported as such, the first cases appearing in the literature in the period 1922 to 1933. During that interval the incidence was 5.0 per cent. This increased to 11.7 per cent in the 1934 to 1946 period.

TABLE VII

Percentage Change in Incidence (1904–1946)—Chronic Fibrous Mediastinitis Group

Time Interval	1904–1911, Incl.	1911–1921, Incl.	1922–1933, Incl.	1934–Jan. 1946, Incl.
Total case reports—Vena caval obstruction	35*	44	60	111
Tuberculous mediastinitis	11.4% (4 cases)	9.1% (4 cases)	8.3% (5 cases)	5.4% (6 cases)
Syphilitic mediastinitis	28.6% (10 cases)	18.2% (8 cases)	13.3% (8 cases)	0.9% (1 case)
Chronic fibrous mediastinitis—"idiopathic"	0	0	5.0% (3 cases)	11.7% (13 cases)

* 8 cases by Rauth not included.

In the early case reports of chronic fibrous mediastinitis (traction or compression by scar tissue), particularly those included in Fischer's series, there is room for considerable diagnostic error, especially in unautopsied cases. The diagnostic measures, so important in differentiating the etiological factors in this group, were not available until the latter part of the 19th century or the first part of the 20th century. Koch announced the isolation of the tubercle bacillus in 1882. Roentgen announced his discovery of the value of the roentgen-ray for diagnostic purposes in 1896, and Wassermann described his complement fixation test for syphilis in 1906. Consequently, it is not peculiar that Fischer's series contained only 6 per cent resulting from traction or compression by scar tissue whereas our series contains 24.8 per cent (table 4).

Chronic fibrous mediastinitis of idiopathic, or non-specific, origin is deserving of detailed consideration. In regard to this group, Erganian and Wade [43] reached the following conclusions: "(1) Occlusion of the superior vena cava is, in a small percentage of instances, due to an anatomic entity designated as chronic fibrous mediastinitis. (2) The gross and microscopic features of the condition are characteristic: a poorly defined mass in the superior mediastinum composed of dense collagenous tissue with foci of infiltration with leukocytes and calcification. (3) Etiologic factors are indefinite, but it seems likely that a mild inflammation of the mediastinum

in an individual with tendency to excessive cicatrization may slowly progress to form the typical dense mass of fibrous tissue."

For the development of the scar tissue there must be some antecedent etiological factor such as upper respiratory infection, influenza, bronchopneumonia, tularemia, trauma, rheumatic fever, plus occasionally a tendency to the development of excessive amounts of cicatricial tissue. We have carefully reviewed this group, taking into consideration possible etiological factors and the time relationship between these factors and the subsequent development of obstruction of the superior vena cava. Histories, in a high percentage of reported cases, reveal an antecedent infection of the respiratory tract, or trauma. The respiratory infection may have occurred months or years before symptoms of obstruction appeared.

Case 1, by Erganian and Wade,[43] developed symptoms five years after skinning some rabbits. At the time of the original infection he showed many of the clinical features of tularemia. Case 2, by the same authors, showed evidence of unusual tendency toward scar tissue formation, as shown by a keloid of a midline abdominal scar. Case 3, by the same authors, showed evidence of vena caval obstruction, beginning one year after a severe respiratory infection with bloody sputum and pleurisy.

Detailed histories are not given by Hinshaw and Rutledge[60]; consequently, the possible etiological factors cannot be reviewed in their cases.

Ochsner and Dixon[89] report a case probably resulting from trauma. There is likewise a history of trauma in case 1, by Gray and Skinner,[55] the injury occurring 10 months prior to the onset of symptoms.

Case 2, by Gray and Skinner,[55] gives a history of several attacks of pneumonia prior to 11 years of age. The patient was 27 at the time of the report. Fibrous tissue and a lymph gland removed at the time of surgery for pathological study showed only chronic inflammatory change.

Strausz[132] reported mediastinal fibrosis 10 years after influenza in a patient 24 years of age.

In our case 1 of chronic fibrous mediastinitis, a female aged 27, the history dates back to five years of age, at which time the patient had bronchopneumonia. Two years later she developed symptoms which apparently were quite characteristic of beginning superior vena caval obstruction.

Lerche[154] has pointed out that mediastinal lymph nodes often become infected as a result of infection of the respiratory tract and preëminently so the tracheo-bronchial groups. He furthermore indicates that in whatever way the microörganisms enter the lungs, they ordinarily are carried off from the lungs and bronchi by the lymphatics of the tracheobronchial lymph nodes. These nodes may serve as important germ harboring depots. Microörganisms may be present in them without other demonstrable foci in the body. Lerche's case 1 seems significant in regard to time interval in which these bronchial nodes may serve as germ harboring depots before suppuration. The patient was a farmer, age 46, who gave a history of a

severe attack of influenza at age 39. Following this illness, he had a persistent, dry, hacking cough. About three months prior to consultation he noted pain in the upper part of the chest, behind the sternum and to the right. After due study a diagnosis of mediastinal abscess due to suppuration of the right tracheobronchial group of lymph nodes was made. Shortly thereafter the abscess ruptured spontaneously into the trachea. Cultures of the pus showed pneumococci predominating. Fibrosis with or without actual suppuration must develop from such a process, and eventually produce vena caval obstruction if properly located. (A sterile abscess was found in our case 1 at the time of surgery.)

The striking uniformity in these histories concerning previous severe respiratory infection or thoracic trauma indicates strong probability that the infection or trauma bears a causal relationship to the subsequent development of "idiopathic," or non-specific, chronic fibrous mediastinitis and eventually superior vena caval obstruction. In view of the probable etiological importance of acute respiratory tract infection and in view of the present effectiveness and availability of sulfonamide and antibiotic therapy, it is reasonable to expect a drop in incidence of this type of mediastinitis in future statistics.

Symptomatology and Clinical Findings

The symptomatology and clinical findings of the syndrome under consideration, except for the primary pathology involved, is secondary to obstruction of circulation in the superior vena cava. This obstruction causes increased venous pressure in that part of the body which normally has its venous return to the superior vena cava, and collateral diversion of the blood stream. There may or may not be delay in circulation time. As a result of this obstruction and the coincidental change in venous pressure, dilated veins are often visible in the upper half of the body, and edema in the upper extremities, head and neck is frequently noted. Often cyanosis and dyspnea are present. Headache and chest pain are commonly troublesome. Other signs and symptoms which are sometimes associated with this syndrome are hoarseness, dysphagia, drowsiness, and occasionally convulsions. The above clinical findings in the presence of elevated venous pressure in the upper extremities, and normal venous pressure in the lower extremities are sufficient to make a diagnosis of superior vena caval syndrome. Further proof can be obtained by diodrast visualization according to the technic of Robb and Steinberg.[107]

Treatment

Treatment of this condition is largely a matter of treating the primary disease. Symptomatic relief may be afforded by repeated phlebotomies; surgical intervention in selected cases may be justified in an attempt to relieve the obstruction, if due to external pressure. The experience of Gray and

Skinner [55] indicates that mediastinotomy with release of constrictive bands is indicated in those cases of superior vena caval obstruction from chronic mediastinitis in which the venous pressure is increasing and in which the symptoms are progressing.

Prognosis

Prognosis is largely the prognosis of the primary disease. Since malignancy and aneurysm are the etiological factors in over 70 per cent of the cases, prognosis naturally is rather poor. Cases in which the etiological factors carry a favorable prognosis may live for years in relative comfort after adequate collateral circulation has been established. This was admirably shown in the cases of Blasingame,[16] Futcher,[51] Meixner,[86, 87] and Mann.[77] The case of Blasingame was 93 years of age, having complete obstruction of the superior vena cava and extensive collateral circulation proved by anatomical dissection. (The anatomical specimen is on display in the Museum of the Department of Anatomy, at the University of Texas School of Medicine at Galveston.)

Our case 1 apparently has had symptoms from vena caval involvement since seven years of age and has developed extensive collateral circulation as proved by surgery and diodrast visualization; however, during much of the time since the onset of symptoms, the patient has been incapacitated.

Case Reports

Case 1. A female practical nurse, age 27, was admitted to the St. John's Hospital on February 8, 1939 for treatment of an acute respiratory infection, which subsided satisfactorily in six days under conservative therapy.

Past History: History was obtained of frequent respiratory infections after the age of five. At five years of age, she had a severe case of bronchopneumonia. Condition at the time was critical and she experienced a prolonged convalescence. Two years later she developed dyspnea of unusual intensity, which she described as asthmatic breathing, during physical exercise. At 14 years of age, a throbbing sensation developed in her head. The troublesome dyspnea on physical exertion continued. At 19 years of age, she first noted swelling of the face and neck, chest pain, and nose bleed. Dyspnea on exertion, head throbbing and pain (especially with the head lowered), chest pain and cough, recurring edema of face, neck, and upper extremities, have been troublesome to date. Her history, otherwise, was irrelevant.

Physical Examination: Patient was well developed and nourished, acutely dyspneic, respirations shallow, skin moderately cyanotic, coughed frequently, and complained of acute substernal discomfort. The external jugular, median basilic, and cephalic veins were unusually prominent, especially on the left side. Her blood pressure was 110 mm. of mercury systolic and 70 mm. diastolic in the arms and 125/85 in the legs. Temperature was 101.2°, pulse 110, respirations 28. The heart was normal, except for moderate tachycardia. There were a few basal râles in the left chest posteriorly and suppressed breath sounds over the entire lung field. Physical examination otherwise normal. Clinical impression was acute respiratory infection with probable mediastinal tumor.

Laboratory Studies: Hemoglobin 90 per cent; red blood cells 4,420,000; white cells 14,000; 85 per cent polys; 15 per cent lymphocytes; Wassermann test negative.

Roentgen-ray studies showed moderate infiltration at the base of the left lung. In the superior mediastinal space a shadow was noted which extended to the right. Radiological diagnosis was probable mediastinal tumor and early bronchopneumonia left base. She was discharged from the hospital February 14 apparently recovered from the acute respiratory infection.

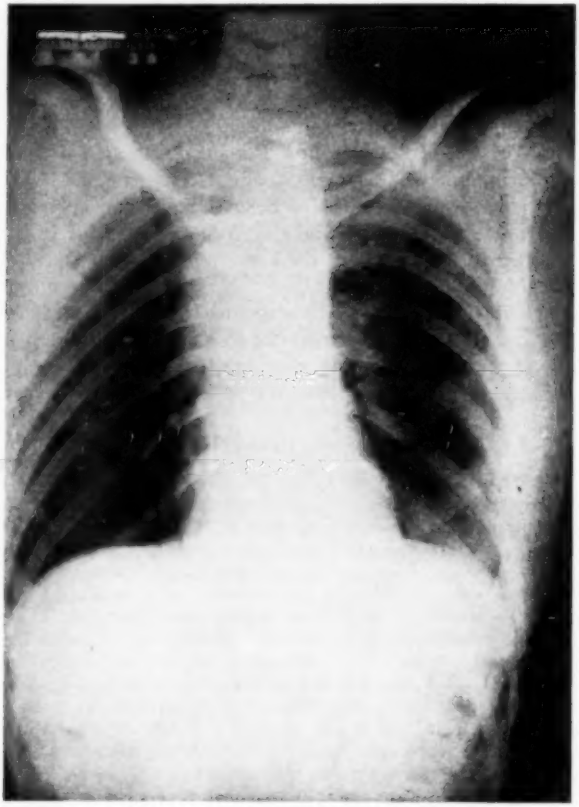

FIG. 5. Chest roentgenogram, February 11, 1939, showing abnormal shadow in right mediastinum. Inflammatory change left base.

On March 9, 1939, she was admitted to the Shannon Memorial Hospital for additional diagnostic studies. Roentgen-ray studies of the esophagus and bronchoscopic examination were both normal. During this admission, a therapeutic trial of radiation was given. This was repeated April 22. No change in the size of the mediastinal tumor was noted following roentgen-ray therapy. Symptomatic change was indefinite.

She was re-admitted to the Shannon Hospital in March of 1940 for treatment of an acute upper respiratory infection, which promptly subsided.

The patient's symptoms of dyspnea, cough, thoracic pain, and headache had persisted. Prominence of the superficial veins and recurring episodes of edema in the upper portion of the body had continued. Cyanosis was prominent. These clinical findings, a persistent mediastinal tumor by roentgenogram, lack of response to radiation, and normal bronchoscopic studies, made it imperative that further investi-

FIG. 6. Diodrast studies, June 20, 1941, showing obstruction of superior vena cava with extensive collateral circulation.

gation be conducted. Consequently, intravenous diodrast studies, according to the technic of Robb and Steinberg [107] were made June 20, 1941. The circulation time, arm to tongue, was 20 seconds. The diodrast studies demonstrated obstruction of the superior vena cava with a large tortuous azygos vein and prominent mammary veins (figure 6). In view of these findings, it was felt that exploratory surgery was indicated, and arrangements were made with Dr. Claude Beck, of Cleveland, for this work.

The patient was admitted to the Lakeside Hospital, Cleveland, April 1, 1942. Her history and physical findings were essentially the same as given above. The hemoglobin was 75 per cent; and the red cells 4,420,000; white cells 7,000; Kline exclusion test negative; vital capacity 3100 c.c.; venous pressure in the right arm, 20 cm.; left arm, 17½ cm.; the left leg was 7.5 cm.; circulation time, arm to tongue, 20 seconds; blood urea nitrogen, 8.3 milligrams per 100 c.c.; urea clearances were normal; intradermal tuberculin test was positive in 48 hours. Roentgenographic studies of the chest showed a rounded mass to the right of the mediastinum opposite the aortic arch, 5 cm. long and 1 to 2 cm. in width. It was located anteriorly in the chest but did not displace the trachea. It did not pulsate. Tentative diagnosis was obstruction of the trachea and superior vena cava, due either to malignant neoplasm or an inflammatory mass.

On the eleventh hospital day, a mediastinal exploration was performed by Dr. Beck. A dense inflammatory mass was found to encircle the superior vena cava and trachea. This was largely removed. At the carina, a small abscess was encountered containing 5 to 10 c.c. of pus. This was evacuated. Powdered sulfathiazole was placed in the cavity. At the end of the operation, the surgeon felt that there was no obstruction to the vena cava and the trachea seemed to be considerably freer.

Her postoperative course was satisfactory until the thirteenth day when she developed pain and tenderness along the course of the right axillary and brachial veins. The following morning she experienced a sudden episode of pain in the chest with dyspnea and cyanosis, rapid pulse and drop in blood pressure. This was believed to be the result of pulmonary embolism originating from the right axillary vein. Continuous heparinization was started and the right subclavian vein was ligated. A few days following the ligation the venous pressure readings were 30 cm. in the right arm and 16 cm. in the left. She gradually improved and was up walking around the ward without much discomfort at the time of her discharge on the forty-eighth hospital day, apparently showing progressive subjective improvement.

Provisional diagnosis was: (1) partial tracheal obstruction due to scar; (2) obstruction of superior vena cava due to scar; (3) sterile abscess of infratracheal lymph nodes.

Pathological Report: Guinea pig injection of pus aspirated from the thoracic abscess was negative for tuberculosis. Histological examination of the tissue removed at the time of surgery showed the following findings as reported by T. C. Laittly, M.D. "Representative sections of the specimen show it to be composed of dense collagenous connective tissue. Throughout, there is evidence of fibrosis and there is considerable infiltration with inflammatory cells, the majority of which are lymphocytes. There are also scattered large round cells, and there are irregular pink fibers that contain granular blue material resembling calcium. There is no tubercle formation, or evidence of malignant tumor in the sections examined.

"Section stains by the Von Kossa method show identifiable calcium in the tissues. Section stains by the Masson-trichrome method identify most of the tissue as collagenous connective tissue of adult type. Section stains by the Ziehl-Neelsen technic show no identifiable tubercle bacilli. Histologic diagnosis is chronic inflammation of fibrous connective tissue with focal calcification and heteroplastic bone formation (mediastinum)."

Follow-up Note: After returning to San Angelo the patient remained symptomatically improved for approximately one year and then gradually developed a return of her previous symptoms of headache, chest pain, nausea and vomiting. The severity of her symptoms gradually increased until they were about the same as before surgery.

In February, 1946, diodrast studies were repeated, according to the Robb and Steinberg [107] technic and showed changes essentially the same as those seen at the first visualization before surgery, the superior vena cava being completely obstructed

(figure 8). Circulation time, arm to tongue, was 20 seconds. The venous pressure reading, left arm, was 35 cm.

In an attempt to relieve headache, a spinal puncture was done. Spinal fluid pressure was 250 mm. of water; 15 c.c. of clear colorless fluid were removed after which the spinal fluid pressure was 150 mm. This gave the patient no relief, in fact, seemed to aggravate her headache. Temporary partial relief was obtained from phlebotomy. Recent bronchoscopic and esophagoscopic examinations showed no

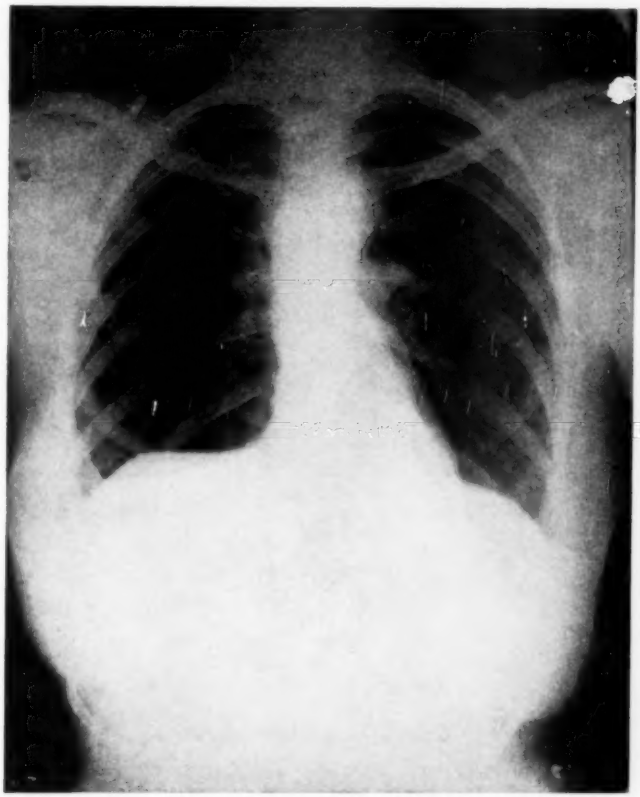

FIG. 7. Postoperative roentgenogram, July 6, 1942, showing reduction in size of mediastinal mass (see figure 5).

evidence of obstruction. She remains on symptomatic measures. Her symptoms are increasingly more difficult to control. Additional surgery has been considered. However, in view of the absence of esophageal and bronchial obstruction, the presence of complete obstruction of the superior vena cava, and the excellent collateral circulation as demonstrated by recent diodrast studies, additional surgery is probably contraindicated. The present venous return seems quite adequate (figures 8, 9 and 10).

This patient apparently is a case of chronic fibrous mediastinitis as described by Erganian and Wade. She demonstrates evidence of gradual obstruction of the superior vena cava over a long period of time, apparently a result of severe respiratory infection in childhood with frequent repeated insults of similar nature since the original episode. This prolonged time interval bears considerable emphasis.

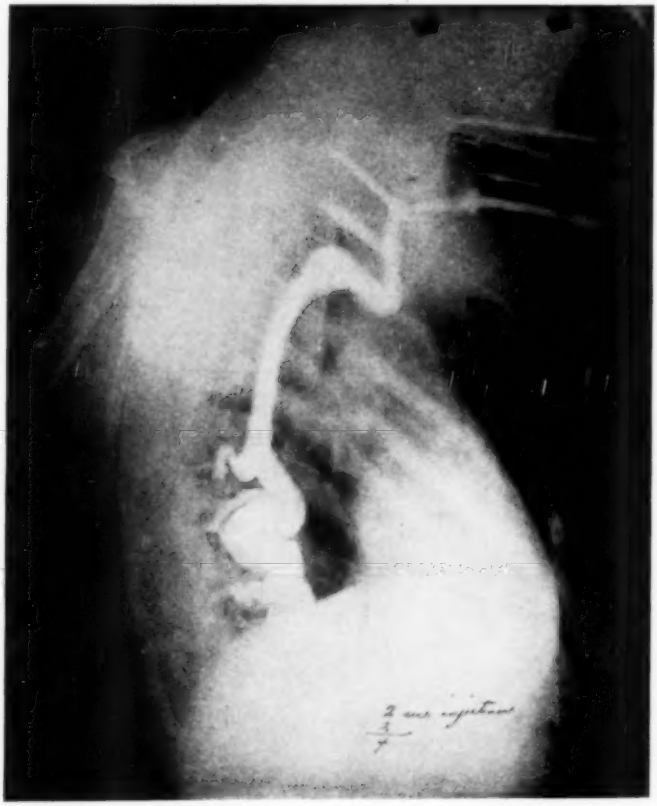

FIG. 8. Diodrast studies, February 20, 1946, showing vena cava still obstructed and the vena azygos enormously dilated and tortuous.

By diodrast visualization a complete obstruction of the superior vena cava and extensive collateral circulation involving particularly the azygos and mammary veins was demonstrated. For the following reasons the obstruction seems definitely to be located below the opening of the azygos into the superior vena cava: (1) diodrast shows continuity between the left

axillary, subclavian, and innominate veins, superior vena cava and azygos (figure 8); (2) the blood flow is clearly in reverse direction around the obstruction, reaching the heart by way of the inferior vena cava. If the obstruction was above the azygos opening, the direction of blood flow would be normal and the azygos would not fill with diodrast.

FIG. 9. Film taken two seconds after the film in figure 8, showing diodrast in lung fields, indicating satisfactory function of collateral system.

This case shows the azygos to be the important collateral system in superior vena caval obstructions below the azygos opening. Robb [156] also was able to visualize by angiocardiograms a similar collateral system in a case with similar point of caval obstruction. Carlson [149] was unable to demonstrate this system experimentally in dogs following ligation of the superior vena cava below the azygos opening. His animals died promptly of respiratory failure following this procedure. However, the two clinical cases cited above prove that superior vena caval obstruction below the azygos

opening is compatible with life. In view of Carlson's work this compatibility is probably dependent upon the time factor, requiring slow development of the obstruction, thereby allowing gradual and adequate formation of collateral circulation.

From an exhaustive review of the literature, this apparently is the only case on record in which coincidental obstruction of the trachea and the

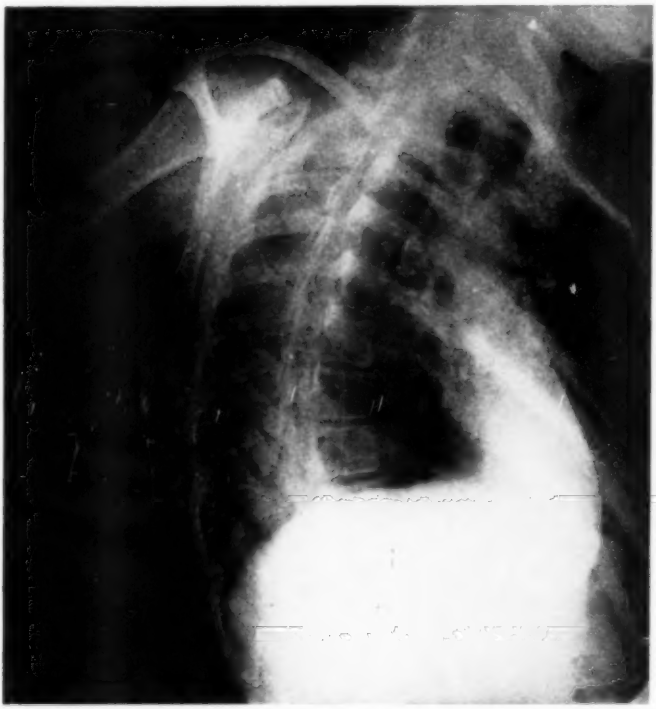

FIG. 10. Film taken February 21, 1946, showing clear lung fields, indicating the shadows in figure 9 to be diodrast.

superior vena cava has been successfully operated upon. A female, age 40, having obstruction of both the superior vena cava and trachea, was operated upon by LeFort,[72] but died during surgery. Postmortem examination showed the obstructing mass to be a lymphosarcoma.

Case 2. M. S., a 29 year old white male, a garage mechanic by occupation, was seen December 15, 1942, complaining of vertigo and a sensation of fullness and pressure in the head and neck when exerting himself or stooping over. He had been well until the spring of 1942, when he suffered an attack of severe chills, feverishness, prostration, cough, and sore throat; he was ill for one week and saw no physician.

In July of that year he developed a vague malaise and noted vertigo when bending forward. These symptoms persisted until October, at which time he undertook a course of vigorous physical exercise and began to feel extraordinarily well. After several weeks, however, the vertigo on stooping returned and he also noticed swelling of the neck and simultaneously a mild choking sensation with dyspnea. Walking about slowly gave some relief; lying supine greatly aggravated the symptoms; a hot shower caused the symptoms to appear. In the two month period, ending in October, the collar size had increased from 14½ to 16. Two days prior to examination he engaged in a friendly scuffle with a fellow employee; he felt his neck swell, he became dizzy and dyspneic, and then, without losing consciousness, "everything went black."

Physical examination revealed a muscular and well nourished man with no abnormal cervical venous distention but with capillary varices over the upper sternum and a flushed face. The neck appeared large but showed no pitting edema and no tumors. Blood pressure in the arm was 150/88, in the leg 162/110. Funduscopic examination and the remainder of the physical examination revealed no abnormalities. Routine blood count and urine examination gave normal results; the basal metabolic rate was minus 9 per cent. A roentgenogram of the chest showed a fairly extensive calcification of both hilar regions with a calcified primary focus in the right lung.

No change in condition occurred during the following two months except that the capillary varices over the sternum became more extensive. Antecubital venous pressure determination taken February 8, 1943, was 17 cm. bilaterally. The latter half of February and the month of April 1943 saw an increase in symptoms and signs: mild exercise produced a greater degree of head fullness, dizziness and dyspnea than formerly; two pillows were necessary in sleeping.

Roentgenograms in April revealed a small traction diverticulum of the esophagus. Adjacent to the diverticulum was a mulberry-like calcification forming a mass 18 by 35 mm. in the right mediastinum opposite the aortic arch. The mass produced a definite paramediastinal bulge and was located just anterior to, and to the right of, the trachea. In this position, it was apparent that the mass and the superior vena cava were in very intimate relationship. There were other smaller calcified densities scattered throughout the mediastinum. The roentgenologist was of the opinion that the observed mediastinal densities represented calcified tuberculous lymph nodes.

Antecubital venous pressure readings, taken April 16, 1943, revealed a pressure of 27 cm. in the right arm, 24 cm. in the left. The lower extremities were normal in color and size, showed no pitting edema nor abnormal venous distention. The external jugular veins were dilated to a height of 12 cm. (vertical) above the manubrium sterni, with the patient in a standing position. The upper one half of the thorax was of a dusky color, the ear lobules were cyanotic, the face flushed, the lips livid, the retinal vessels moderately dilated, and the conjunctivae suffused. Many purplish tortuous capillary varices were present over the sternum, around the nipples, and on the lower anterior and lateral thorax bilaterally; less marked varices of the same type were found extending from the lower neck over the clavicle toward the sternum. Blood pressure in the arm was 132/78. The circulation time, using calcium gluconate in the "arm to throat" test, was 10 seconds.

This man has not been seen since April 1943. The etiology of the caval obstruction remains obscure. There are three possibilities: (1) chronic fibrous mediastinitis resulting from antecedent respiratory infection some three or four months prior to onset of symptoms, (2) chronic fibrous mediastinitis of tuberculous origin, (3) traction diverticulum of the esophagus. The evidence at hand favors chronic fibrous mediastinitis from respiratory infection. At least the causal relationship of this factor as regards time interval seems quite definite.

Both cases which we have reported emphasize the apparent etiological importance of respiratory tract infection in the development of chronic fibrous mediastinitis. On the basis of known facts pertaining to anatomy and bacteriological and pathological reactions, the theoretical sequence of events in such cases is: (1) respiratory tract infections (usually pneumonia); (2) lymphadenitis of mediastinal lymph node chains; (3) perilymphadenitis; (4) healing or chronicity with mediastinal fibrous tissue deposition; (5) cicatricial tissue contraction and partial obstruction of the superior vena cava; (6) thrombosis of superior vena cava, if the lumen becomes quite narrow and the intima becomes damaged or irregular.

Discussion

Available historical data indicate that William Hunter, 1757, published the first authentic account of a case of obstruction of the superior vena cava.

In the literature since 1904 there are at least 250 cases of superior vena caval obstruction.

Collateral diversion of the blood stream in the upper one-half of the body is responsible for some of the prominent clinical manifestations of the condition in question. The four principal collateral systems involved are defined and are presented in one composite, schematic representation, thereby showing their interrelationship and their relative importance in superior vena caval obstruction at different levels.

The anatomy of the mediastinum as regards the relationship of the superior vena cava to the ascending aorta, right bronchus, and lymphatic system is emphasized. The importance of disease of these structures in producing superior vena caval obstruction is indicated. It is shown that most of the structures of the right thoracic cavity and a part of the structures of the left thoracic cavity and mediastinum eventually drain into either or both the right anterior mediastinal and the right latero-tracheal lymphatic chains. The frequency of neoplastic and inflammatory disease in this part of the body is a constant threat to these lymph glands with possible obstruction, partial or complete, of the superior vena cava from extrinsic pressure or invasion. Chronic fibrous mediastinitis may result from inflammatory involvement.

So-called "idiopathic," or non-specific, chronic fibrous mediastinitis is probably secondary to such factors as trauma and pulmonary infection, particularly the latter, in a high percentage of cases. The time interval between the pulmonary infection and development of superior vena caval obstruction may be months or years.

There is a dramatic drop in incidence of syphilitic mediastinitis from 28.6 per cent to 0.9 per cent during the period 1904 to 1946. This apparently is a result of improved methods in the diagnosis and treatment of syphilis. There is a definite but less dramatic drop in incidence of tuberculous mediastinitis. Chronic fibrous mediastinitis of unknown cause was not

reported as such prior to the 1922 to 1933 period. From 1922 to 1946 the incidence increased from 5 per cent to 11.7 per cent. In view of probable importance of acute respiratory tract infection in the etiology of idiopathic, or non-specific, chronic fibrous mediastinitis and in view of the present effectiveness and availability of sulfonamide and antibiotic therapy, it is reasonable to suppose that future statistics will show a definite drop in incidence of this condition.

The etiological factors are tabulated, giving bibliographic references for each factor, and case reports divided into verified and unverified groups covering the period 1904 to January, 1946, inclusive. Comparisons are made with Fischer's series prior to 1904 and composite figures for both series tabulated. These tabulations indicate that 75 to 80 per cent of cases of superior vena caval obstruction are due to chronic mediastinitis, malignant primary thoracic tumors, and aneurysms.

Although there are conflicting opinions, there is considerable evidence that obstruction of the superior vena cava is not uncommon. The frequency of space occupying lesions of the mediastinum, the anatomical relations of the superior vena cava, the easy compressibility of this vessel, and the increasing number of case reports in the literature indicate that the syndrome probably occurs not infrequently.

Two cases of chronic fibrous mediastinitis are presented, one verified by surgery, both apparently a result of previous acute respiratory tract infection.

In case 1 the point of obstruction of the superior vena cava is demonstrated by angiocardiograms to be below the azygos opening, proving the lesion in this location to be compatible with life. The azygos is shown to be the important collateral system in caval obstructions below the azygos opening.

Summary

Literature for the period 1904 to 1946 was reviewed and 250 authentic cases of obstruction of the superior vena cava were found, 145 verified by autopsy or surgery.

Bibliographic data are tabulated according to etiology (table 3). Comparisons are made with Fischer's collection of 252 cases prior to 1904 and composite figures presented covering total incidence of important etiological factors in 502 cases from the world's literature to January 1946 inclusive.

The first authentic case report was by William Hunter in 1757.

Applied anatomy of superior vena caval obstruction is presented and particular emphasis given to collateral circulatory routes and the mediastinal lymphatic system.

Trends in etiology in the past four decades are discussed.

Special consideration is given to idiopathic, or non-specific, chronic fibrous mediastinitis and two case reports of superior vena caval obstruction resulting from this condition are presented. In one, the point of obstruction

is below the azygos opening into the superior vena cava and the principal collateral system is shown to be the azygos.

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THE URINARY EXCRETION OF CREATINE IN ARTHRITIS *

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The investigation here reported was undertaken to ascertain whether or not there was any abnormal excretion of creatine in rheumatoid and osteoarthritis. Within the last decade, creatine metabolism has been the object of very extensive research. The mechanism of the intermediate metabolism of creatine has not yet been elucidated completely. Evidence, however, exists to favor the view that glycine is converted to guanidinoacetic acid which is then methylated to form creatine.[1] The first of these reactions probably takes place principally in the kidney and the transfer of free methyl groups occurs chiefly in the liver.

Considerable material has been gathered with regard to the occurrence of creatinuria under physiological and pathological conditions. It is present in childhood.[2] It is common in normal adult women especially during and immediately after the menstrual period.[3] While some authors have found no urinary creatine in the normal adult male, others have found creatinuria up to 200 mg. a day.[4, 5, 6] In an experiment it was shown by Taylor and Chew [6] that the protein intake had no influence on the creatine excretion. Primarily, creatinuria is encountered in progressive muscular dystrophy, tabes dorsalis, transverse myelitis, spinal cord tumor, encephalitis, chorea and myasthenia gravis. It is also frequent in febrile diseases, carcinoma, cirrhosis of the liver, cardiac failure, diabetes mellitus and hyperthyroidism.[3, 7, 8]

Clinical Material

The material selected consisted of adult male and female subjects with no evidence of neurological involvement. During the period of the study the patients were on an ordinary diet. Four groups of subjects were studied. The first comprised 10 young adults, all normal. The second group of 10 patients varied in age from 48 to 87 years, and were relatively normal. The third group consisted of 10 patients under treatment for rheumatoid arthritis. The last group comprised 10 patients suffering from osteoarthritis. None of these subjects had any condition previously noted which might complicate the results.

Method

All the subjects were on a regular diet and performed no unusual exertion on the day of the test. At 7:00 a.m. on the morning of the test, the bladder

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was emptied and the urine discarded. From 7.00 a.m. to 7:00 a.m. the following day the urine was collected and preserved with thymol. Specimens containing protein, sugar, or formed elements were not accepted. Urinary creatine was determined by the method of Folin.[9]

Results

Table 1 shows that on an unrestricted diet, in 10 normal healthy male and female adults, 18 to 33 years of age, the 24 hour creatine excretion varied from 85 mg. to 280 mg. These subjects were free from any infection or other diseases and performed no unusual exercises during the period of the test. The average 24 hour creatine excretion was 161 mg.

Table I

24 Hour Urinary Creatine Excretion In 10 Young Healthy Adults

Case	Sex	Age	Volume	Creatine
1	F	18	1425 c.c.	280 mg.
2	M	23	1520 c.c.	161 mg.
3	F	21	950 c.c.	143 mg.
4	M	24	1310 c.c.	104 mg.
5	M	23	1220 c.c.	268 mg.
6	F	26	1670 c.c.	114 mg.
7	F	20	1330 c.c.	119 mg.
8	M	25	850 c.c.	85 mg.
9	F	33	2150 c.c.	129 mg.
10	M	28	1150 c.c.	207 mg.
				Average 161 mg.

Table 2 shows that the 24 hour creatine excretion in 10 elderly subjects, 48 to 87 years of age, varied from 63 mg. to 351 mg. of creatine. The average 24 hour creatine excretion was 185.1 mg.

Table II

24 Hour Urinary Creatine Excretion In 10 Elderly Healthy Adults

Case	Sex	Age	Volume	Creatine
1	F	67	1440 c.c.	115 mg.
2	M	50	1280 c.c.	280 mg.
3	F	65	900 c.c.	171 mg.
4	F	63	1800 c.c.	270 mg.
5	F	87	700 c.c.	70 mg.
6	M	55	1050 c.c.	63 mg.
7	F	64	870 c.c.	235 mg.
8	M	48	1300 c.c.	351 mg.
9	M	72	1800 c.c.	198 mg.
10	F	58	1620 c.c.	98 mg.
				Average 185.1 mg.

Table 3 shows that in 10 patients with rheumatoid arthritis, 31 to 62 years old, who had the disease from 1 to 20 years, the 24 hour urinary creatine excretion varied from 40 to 358 mg. and the average excretion was 175.9 mg. in 24 hours. In patients 8 and 10 it was observed that as the condition improved on gold therapy, the creatine excretion increased and was concomitant with a gain in weight and an improved sense of well being.

TABLE III

24 Hour Urinary Creatine Excretion In Rheumatoid Arthritis

Case	Sex	Age	Duration	Creatine
1	F	38	13 years	216 mg.
2	F	34	8 years	98 mg.
3	F	53	20 years	252 mg.
4	F	62	5 years	196 mg.
5	M	41	7 years	40 mg.
6	F	36	12 years	91 mg.
7	M	31	1 year	76 mg.
8	F	45	10 years	262 mg.
9	M	62	6 years	170 mg.
10	F	35	10 years	358 mg.
			Average	175.9 mg.

There appeared to be no correlation between the creatine excretion, blood cholesterol or sedimentation rate. Neither age nor the duration of the disease had any effect on the creatine output. In spite of the widespread nerve and muscular changes characteristic of rheumatoid arthritis, the average 24 hour creatine excretion in the 10 patients was within normal limits. Two

TABLE IV

24 Hour Urinary Creatine Excretion In Osteoarthritis

Case	Sex	Age	Duration	Creatine
1	F	65	10 years	1498 mg.
2	F	44	3 years	719 mg.
3	F	36	9 years	639 mg.
4	M	50	10 years	741 mg.
5	F	59	2 years	611 mg.
6	M	68	15 years	700 mg.
7	M	70	40 years	434 mg.
8	F	72	10 years	448 mg.
9	F	53	1 year	502 mg.
10	F	56	1 year	462 mg.
			Average	675.4 mg.

daily creatine determinations on a case of lupus erythematosus disseminatus were found to be within normal limits (262 mg. to 175 mg.).

In table 4 the youngest patient was 36 years and the oldest 72 years. The osteoarthritis had been present in these cases from one to 40 years. All of these patients had a normal sedimentation rate (Westergren). Here, the

creatine excretion varied from 434 mg. to 1498 mg. in 24 hours. The average 24 hour creatine excretion was 675 mg. None of these patients had any dietary restrictions. Alpha-tocopherol in large doses (300 mg. daily) was used for three months in the last three patients with no clinical improvement and with no effect on the creatinuria.

Discussion

From the evidence it appeared that creatinuria was a normal process in the adult male and female and that it occurred in all the age groups of the above investigation. In tables 1 and 2 the average normal 24 hour urinary creatine was less than 200 mg. It is stated that "creatine is normally absent from the urine of men." [10] Creatine was never absent in any of the groups. It is possible that inadequate methods and lack of proper equipment could explain the failure of earlier workers to observe creatinuria in the normal adult male.[11]

Table 3 indicated that this group with active rheumatoid arthritis had a normal creatine excretion.

Table 4 showed an increase in the average creatine excretion for the patients with osteoarthritis. The creatinuria could not be explained by muscular atrophy since very few of the patients examined showed any signs of this condition.

Conclusions

In a young group of 10 normal subjects ages 18 to 33, male and female, the average creatine excretion was 161 mg.

In an older group of 10 healthy subjects whose ages varied from 48 to 87 years the average 24 hour creatine excretion was 185.1 mg.

The average creatine excretion in 10 subjects with active rheumatoid arthritis was 175.9 mg.

In 10 patients with osteoarthritis, the 24 hour creatine excretion averaged 675.4 mg.

The possibility is presented that in osteoarthritis there exists an abnormal excretion of creatine.

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NEUROCIRCULATORY ASTHENIA *

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THE more symptoms a patient complains of, the less the significance of each. Every paper on the subject of Effort Syndrome from the day of DaCosta [1] to the present,[2, 3, 4, 5] has stressed the multiplicity of the symptomatology. MacKenzie [6] has pointed out the difficulty in describing the most common forms of disease, perhaps because of the fact emphasized by Starr [7, 8] that it may be no disease but an exaggerated physiology or what has been referred to in a previous publication [9] as a physiogenic form of abnormality of adjustment. Starr ingeniously compares effort syndrome with ordinary clumsiness of muscular movement inferring that his ballistocardiographic studies are an excellent method of studying objectively this particular clumsiness of the circulation. He further states [10] that the group ordinarily diagnosed as neurocirculatory asthenia shows an incoördination of the circulation which brings his analogy from mere clumsiness toward what might be termed "ataxia" of the circulation. And it is true that all variations are seen from mildly exaggerated physiological response to exercise to a state of extreme disability.

Levy, Stroud and White [11] in their reëxamination of men disqualified for military service because of cardiovascular defects found that 17.3 per cent could be reclassified as fit for duty. They felt that neurocirculatory asthenia was a legitimate cause for rejection and this condition accounted for 4.9 per cent of those rejected for cardiovascular defects. In our experience neurocirculatory asthenia accounts for 6.8 per cent of the admissions to the cardiovascular section of a large general hospital in the United States; 4.6 per cent of the admissions to a comparable unit in the European Theater of Operations and 6.3 per cent of the admissions to the cardiovascular section of a Regional Hospital in the United States. These figures are based on the admission of 30,000 patients. Many of these patients were referred to the cardiologist by the neuropsychiatrists and from other wards in the hospital. Those with manifest anxiety were usually received on the neuropsychiatric wards with a label of combat exhaustion. These cases were usually seen with the psychiatrist and treated with the other cases of exhaustion. If symptoms were severe and persistent they were given a careful cardiac examination with electrocardiographic, phonocardiographic [9] and fluoroscopic methods to determine the presence or absence of organic heart disease.

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Analysis of Data

In 75 per cent of the cases the duration of the disease was 10 years or more and consequently was felt to have existed prior to enlistment. In the remaining 25 per cent the condition had not caused symptoms prior to military service. In many cases the individual had been limited in his physical activity prior to entering the army and he had chosen to follow a more or less sedentary job probably because attempts at hard work had shown him to be poorly fitted for such occupation. This is consistent with the findings of Lewis,[8] Starr [8] and others.[12]

In the entire series there were 576 patients admitted with a diagnosis of neurocirculatory asthenia or effort syndrome. These were classified into one of the following groups:

I. Those with stigmata of constitutional inadequacy.
II. Those with poor physical endowment plus anxiety.
III. Those with primary neurotic manifestations.

It was recognized that no sharp line of distinction could be drawn but by far the majority, 69 per cent, fell into the Group II description and this was much more apparent among those received in hospitals in the European Theater either before entering combat or those who quickly broke down when thrown into combat. In Group I were 14 per cent more of whom were seen in the United States, and 17 per cent fell into Group III about half of whom were seen in the United States and the other half in the combat zone.

By far the majority, 77 per cent, were of the asthenic type and inclined to be underweight as judged by standards of the Medico-Actuarial Mortality Investigation.[13] The average age was 24.7 years. They averaged 8.9 pounds below ideal weight. A few, 8 per cent, were above normal weight and 15 per cent were within normal range. There was no great increase in the number of previous severe infections in this group as compared to other hospital patients, but 8 per cent gave a history suggestive of rheumatic fever or severe sorethroat, and 12 per cent considered themselves subject to "colds" and upper respiratory infection. A fair number of those with neurocirculatory asthenia had been previously hospitalized for jaundice, pneumonia or shell-fragment wounds (21 per cent). Very few of these men, 11 per cent, had been told at some time previously that they had a heart murmur or that their blood pressure was a little too high. A few, 3 per cent, had been kept in bed for a prolonged period because of supposed "heart disease" as a child or prior to their army service.

A considerable number of patients, 19 per cent, gave a history of acute onset of symptoms following sudden exertion or excessive physical strain such as is involved in combat and extreme hardship. Of these the majority occurred early in their combat experience. A good many became conscious of their first symptoms coincident to sea-sickness while the mere threat of going into combat was frequently enough to precipitate the initial attack.

In the majority of these cases there was a great blending of emotional and physical factors either of which was sufficient to explain the reaction.

A small number of patients, 4.2 per cent of the total, showed evidence of a co-existing cardiac lesion. The order of incidence was as follows: mitral stenosis, aortic insufficiency, congenital heart disease, cardiac enlargement, paroxysmal auricular tachycardia, paroxysmal auricular fibrillation, ventricular extrasystoles, and hypertension.

Symptomatology

A fairly large number of the patients seen in the combat zone also suffered with trench-foot or frost-bite (21 per cent) and it seemed to some observers that there was an etiological relationship between the two pathological conditions. Some of the psychiatrists considered that the patient with neurocirculatory asthenia would be hyper-susceptible to trench-foot or frost-bite because of his maladjusted circulation. In fact cold feet was a common complaint among these patients, often a more bitter complaint than the breathlessness that is usually considered the most common symptom. Breathlessness and hyperventilation at rest did occur in some cases but was not as common as reported by others.[14, 15] With exertion breathlessness was a constant symptom and this could often be simulated by excitement. Response to exercise was always poor and the Schneider Index [16] is useful in bringing out the orthostatic hypotension and poor index which will almost always be below 5. The greater the exercise the more severe the symptoms. They are almost completely relieved by rest. This is the reason the term "physiogenic" has been suggested because the symptoms are easily produced physiologically and can be relieved the same way.

Fatigue and exhaustion are often apparent in the facial expression and in the weakness manifest by a general droopiness in posture and activity. The tremor and shakiness increase with the degree of fatigue. Lightheadedness, a feeling of faintness, and mild subjective vertigo were common, often precipitated by the erect posture and/or exercise and relieved by rest in the recumbent position. These symptoms were usually readily produced by the performance of the tilt-table test.[9, 17] In fact, in the early portion of our series it was considered almost a prerequisite to the diagnosis of neurocirculatory asthenia to produce the syndrome in the tilt-position.[9] Haldane [18, 19] states that the abnormal breathing observed in neurocirculatory asthenia is due to fatigue of the respiratory center induced by anoxia.

In a series of well written articles, Friedman [20] has brought forward the thesis that the symptoms of neurocirculatory asthenia stem from hypothalamic dysfunction which in turn causes an excitation of the sympathetic nervous system as described by Fraser and Wilson [21] in their study of the pathogenesis of the syndrome. Cannon [22] pointed out the similarity between neurocirculatory asthenia and the fear or rage reaction in animals following stimulation of the sympathetic nervous system. Friedman has also similarly explained the profound vasoconstriction as a cause of the hyperthermia

and giddiness so frequently complained of and noted by Lewis,[3] Cohn,[23] and Parkinson [24] in accordance with the concepts promulgated by Ransom.[25]

Precordial pain was a complaint in 56 per cent of the cases in this series. It was usually described as occurring in the left side of the chest and more often than not it was an aching or a feeling of soreness accompanied by hyperalgesia. Among those cases seen in the combat zone there was a definite tendency for the pain to be described by the patient in accordance with the lay ideas of angina pectoris or to mimic the stories given by patients with definite coronary disease when it was learned that this frequently led to a transfer to a hospital in the zone of the interior (United States). Sometimes these stories were actually of textbook clarity and were, therefore, of little value in actual assessment of disability. The multiplicity of symptoms and the clinical evidence of either neurocirculatory asthenia or organic heart disease had to be depended upon in a large measure for accuracy in diagnosis. Palpitation, fainting, giddiness, sweating, acrocyanosis and other peripheral signs were of great value in the differential diagnosis.

Electrocardiographic changes, while not specific,[26, 5, 9, 27, 28, 29, 15] were indeed helpful especially when a maneuver such as the erect position, tilting, Schneider Index, and other functional tests were utilized. In this series of cases 35 per cent showed some deviation from normal in records taken before and after exercise or before and after tilting.

Physical signs were usually limited to tachycardia and tachypnea, overactive heart action, unstable blood pressure, a quick and often roughened first heart sound at the apex, cold sweating extremities, and gross evidence of anxiety such as fluttering eyelids, tremor, pallor of the face, excessive pulsation in the neck, insomnia, and nightmares. There may be co-existing neurasthenia, hypochondriasis, hysterical substitution or conversion. Mild depression or mental irritability may predominate.[30] Knehr, Dill and Neufeld [31] feel that blood lactate studies may be useful in the determination of cardiovascular fitness. The studies of Robinson and Harmon brought out a fairly clear distinction between the findings in young men with poorly adaptable circulatory systems and first class athletes.[32] MacLean [33] treated patients with unstable vasomotor systems manifesting orthostatic tachycardia and hypotension by the use of the "head-up" bed and increased salt intake with marked improvement in their adaptation to the erect posture. This phenomenon further substantiates the opinion that disturbed physiology exists in this condition and that the symptoms are physiogenic in origin.

Increased interest in the disturbed physiology of individuals who are subject to neurocirculatory asthenia has followed the demonstration by Cobb, Cohen and Badal [34] of the increased number of twisted capillaries in the nail folds of 48 patients studied. This discovery brings to the fore once again that we are dealing with a condition in the "borderland of disease" to quote Lewis,[3] which when thoroughly understood constitutes an ideal psychosomatic disease for the coördinated study of physiologists, psychiatrists, psychologists, neurologists, endocrinologists [35] and internists.

Principles and Methods of Treatment

It was certainly with pardonable pride that Sir Thomas Lewis [36] refers to his greatest contribution to what is now called Physical Medicine Rehabilitation, as follows: "It was at Hampstead that a system of graded drills was first introduced, and later I employed these to the full both remedially and as a means of justly grading soldiers returned to hospital for supposed affections of the heart. It was my repeated contention that the surest means of gauging physical fitness and endurance is to employ direct tests." This method was utilized both in this country and abroad in the handling of patients with neurocirculatory asthenia. The results were gratifying and effective almost in direct proportion to the completeness with which the original medical work-up was accomplished and the thoroughness of the examiner as well as his powers of persuasion and ability to establish rapport with his patients. It was found to be an excellent policy in our series as well as those treated by Hill and Dewar [37] to forbid further medical examinations or the taking of pulse rates, blood pressure or temperature once the original complete examination was finished. This gave no further suggestion to the patient that anything but recovery was expected. Graduated physical exercise and reassurance by all concerned was the keynote of treatment. Exercises were started with easy drill and physical exercise under careful supervision. Progress was required but it could be slow for some groups and more rapid for others.[38] Group psychotherapy [39] was found to be most helpful in the hands of physicians possessed of the necessary orientation and ability. Privilege rewards for accomplishment were considered extremely helpful in keeping up the interest of participants. Cases not making satisfactory progress were counseled by the psychiatrist and those responding well were discharged from the hospital without further examination. A fairly high percentage of the Group III cases required transfer to a Neuropsychiatric Rehabilitation Center.[40]

Results

It has been impossible to follow-up all of the cases reported in this paper. The immediate results of treatment were gratifying. Of the cases seen in the United States during the years 1941 and 1942, the large majority (72 per cent) were discharged from military service,[41] while 20 per cent were sent to limited duty and 8 per cent were returned to full duty. In the European theater, 40 per cent were returned to full duty, 16 per cent to limited duty, 33 per cent were referred to the neuropsychiatric rehabilitation center, and 14 per cent were returned directly to the United States. From reports received from the neuropsychiatric rehabilitation center where more adequate and longer periods of treatment for the underlying anxiety were undertaken, the total number returned to duty, either light or full military duty, would approximate 75 per cent. No figures are available by which it could be determined how many of these cases relapsed after treatment but

it was not unusual for us to treat the same veteran a second time after his original return to duty. By far the majority of these men responded well to treatment and when returned to duty fairly soon seemed to adapt better. Prolonged hospitalization and separation from their combat unit disturbed their morale and prolonged their rehabilitation.

Summary

The pathogenesis of neurocirculatory asthenia has been studied by a great many careful observers and specialists in various fields of medicine. That the symptoms can be produced physiologically in susceptible individuals has been shown conclusively. It has also been shown that the symptoms are usually relieved by physiological rest and measures directed toward improved physical adaptation. Methods for the detection and differential diagnosis have been discussed and the problem from a military standpoint is reported. Experience with a large number of patients suffering with this manifestation of a psychosomatic disease has undoubtedly served to familiarize many physicians with a practical method of dealing with these daily problems.

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TREATMENT OF MALIGNANT DISEASE WITH NITROGEN MUSTARD *

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Our purpose in this paper is to summarize the clinical literature on the use of the nitrogen mustards in malignant diseases,—the indications, hazards, effects and side-effects. Our experience with 64 additional cases is included.

Reports on the clinical application of the nitrogen mustards in the treatment of neoplastic diseases have recently been released.[1] Rhoads [4] summarized the results of therapy as follows:

1. Methyl-bis (β-chloroethyl) amine hydrochloride (designated HN2) appears to be preferable to tris (β-chloroethyl) amine hydrochloride as venous thrombosis is less likely to follow at the injection site.

2. The recommended dosage is 0.1 mg. per kilogram intravenously on four successive days. Larger doses proved to be hazardous.

3. The toxic effects noted are:

   A. Local
      1. Severe local inflammatory reaction if extravasation into the tissues occurs.
      2. Thrombosis and thrombophlebitis.
   B. Systemic
      1. Nausea and vomiting occurring one to eight hours after a single dose and continuing for three to 24 hours; occasional diarrhea.
      2. Damage to the blood forming organs, characterized by
         (a) Leukopenia (lymphopenia followed by neutropenia)
         (b) Normocytic anemia
         (c) Thrombocytopenia, at times accompanied by bleeding.

4. Cure of neoplastic diseases has not been observed; tumor regressions have been only temporary, rarely extending beyond several months.

The most favorable results, according to Rhoads, have been obtained in the treatment of Hodgkin's disease. Improvement, evidenced by reduction in the size of lymph nodes, disappearance of fever, feeling of well-being and weight gain, usually continued for from two weeks to a few months, followed by fairly rapid relapse. Relapses often responded to further chemotherapy, but remissions were progressively shorter in duration. The

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liver and spleen usually regressed only slightly in size. Large masses of matted lymph nodes, invasion of the disease beyond lymph nodes, and bone lesions often did not show a favorable response even though symptomatic improvement occurred. Skin lesions due to Hodgkin's disease responded variably, and pruritus was only occasionally and slightly relieved. In late, roentgen-ray-refractory cases, HN2 was occasionally of benefit. Highly malignant lymphosarcoma usually failed to respond. Most cases of giant follicular lymphoblastoma improved, but the Committee on Growth recommended local roentgen-ray therapy as the treatment of choice. Acute lymphoblastic and myeloblastic leukemias were not influenced by the drug. Chronic lymphatic leukemia usually responded with a reduction in the white count, decrease in size of the lymph nodes, with somewhat less effect on the hepatosplenomegaly. Since a fall in hemoglobin may also occur, the drug was not recommended in far advanced cases with severe anemia. Chronic myelogenous leukemia was usually similarly affected, but Rhoads preferred local roentgen irradiation for greatly enlarged spleens. Results with polycythemia vera were comparable to those obtained with radioactive phosphorus. Suggestive favorable experience with the production of temporary symptomatic remissions in anaplastic carcinoma of the lung has been reported. Melanosarcoma, metastatic mammary and uterine cervical carcinoma, and multiple myeloma have not responded favorably. Two cases with metastatic sympathicoblastoma [3] responded with rapid reduction in the size of the tumor masses; but remissions were only short-lived.

Jacobson et al.[3] determined urea clearance, plasma proteins, albumin and globulin ratio and cholesterol (total and esters) before and after treatment. No significant changes were noted, whether or not the original values were abnormal. These observers reported leukopenia beginning within 24 hours after the first injection and progressing for three to eight days. Recovery from the leukopenia was not influenced by pentnucleotide, ferrous adenylate, leukocytic extract, or folic acid. Despite marked leukopenia, infection occurred in only one of 59 cases. The infection responded satisfactorily to penicillin therapy. Urobilinogenuria indicated significant increase in hemolysis, but the hemoglobin rarely fell significantly except in polycythemia. The reticulocyte count regularly fell below 0.1 per cent. Marked thrombocytopenia occurred variably. Marked aplasia of the bone marrow, always followed by regeneration, was common. In a supplementary report, Jacobson's group [5] reported on the quantitative findings in sternal marrow aspirates in five cases treated with HN2. The nucleated cell count fell to a minimum during the first two weeks and returned to normal by the sixth week. These authors noted many giant granulocytes in the peripheral blood during the first week.

Goodman et al.[2] whose 67 cases of Hodgkin's disease, leukemia and allied disorders are included in Rhoads' [4] summary, drew particular attention to the usually good results in the treatment of Hodgkin's disease even when the disease had become refractory to radiation. Of 13 patients with lympho-

sarcoma, nearly all in advanced, radio-resistant stages, five failed to improve and in the others the remissions lasted from three weeks to several months; but with each recurrence the course of nitrogen mustard proved less effective and the remission produced was shorter-lived. The authors also found that repeated urinalysis, renal and liver function tests and blood chemistries failed to indicate any change due to therapy with the nitrogen mustards. In the two patients who were treated with more than 0.1 mg. per kilogram for three to six doses (maximum single dose 8 mg.), "toxic hemopoietic effects were observed in the following sequence: the complete disappearance of circulatory lymphocytes, definite leukopenia and granulocytopenia (without mucosal lesions or other signs or symptoms of agranulocytosis except fever), thrombocytopenia of severe grade with purpura, and moderate anemia. Repeated blood transfusions were necessary, and the return of blood values to pre-treatment levels required several weeks."

Wintrobe et al.[5] treated 77 cases of lymphoma with doses varying from 0.1 mg. to 0.25 mg. per kilogram daily in courses of four to eight injections. There were no toxic deaths. Their results were in general agreement with those reported by other members of the group coöperating with the Committee on Growth as detailed above. Two patients with metastatic carcinoma responded with temporary regression of metastatic nodes and improvement in symptoms. The authors noted promising results with the use of "maintenance therapy," consisting of two injections every two to six weeks in lymphomatous patients in remission.

The several series reported above were studied in coöperation with the Committee on Growth and formed the basis of Rhoads' summary.[4] Several smaller series have been reported independently. Alpert and Peterson[6] treated 23 cases of malignancy. Their 15 cases of Hodgkin's disease showed variable response. Post-treatment biopsies revealed necrosis of the reticulum cells, Sternberg-Reed cells and eosinophiles. One case of bronchogenic carcinoma responded with slight shrinkage of the tumor and clearing of hydrothorax, but death from metastases ensued. ApThomas and Cullumbine[7] obtained remissions averaging two months' duration in 21 cases of Hodgkin's disease treated with HN2. They found that 0.2 to 0.3 mg. per kilogram for two days produced the same effects as 0.1 mg. per kilogram for four days with the advantage of fewer days of discomfort for the patient. The two patients treated with 0.2 mg. per kilogram for four days developed severe leukopenia (below 1,000 per cu. mm.), but the counts returned to normal in two weeks without untoward symptoms. Osborne et al.[9] treated five cases of cutaneous lymphomatous disease. They noted marked temporary improvement in mycosis fungoides and cutaneous lymphosarcoma, but no response in the one case of Kaposi's sarcoma treated. They noted marked improvement in a case of chronic disseminated lupus erythematosus. Kierland and Shullenberger[10] also treated six cases of mycosis fungoides with improvement in five for periods up to four months. Taffel's[11] observations on 16 cases of neoplastic diseases are in agreement with those

reported previously. He administered the standard dose of 0.1 mg. per kilogram. Six patients developed pronounced thrombocytopenia, with hemorrhagic phenomena in five. Included in this series were one case of embryonal carcinoma of the testis and one case of fibrosarcoma of the chest wall. Neither patient was benefited by HN2 therapy. An adolescent with a metastatic Ewing tumor of the pelvic bone improved slightly after HN2 treatment, but relapsed promptly.

Clinical Results

This paper reports our observations in the treatment of 64 cases of malignant diseases with HN2 * in the period between July 1946 and January 1948. The cases may be classified as follows: 24 Hodgkin's disease, four chronic lymphatic leukemia (including one associated with lymphosarcoma and one with Hodgkin's disease), two chronic myelogenous leukemia, 10 carcinoma of the lung, two Wilms' tumor, one carcinoma of the breast with generalized metastases, one anaplastic metastatic carcinoma, one melanocarcinoma, eight lymphosarcoma, two mycosis fungoides, one chronic nonleukemic myelosis, three reticulum cell sarcoma, one spindle cell sarcoma, one miliary tuberculosis, one Boeck's sarcoid, and two malignancies of undetermined nature. All of these patients were treated with methyl bis (β-chloroethyl) amine (HN2) in the usually recommended dose of 0.1 mg. per kilogram on each of four successive days, except for eight patients who received 10 mg. daily for four consecutive days. Twenty patients received from two to six courses. In the first half of the series complete blood counts and urinalyses were performed daily, sternal myelograms were performed before, immediately after, and two weeks post-treatment, as were bleeding studies, liver and renal function tests, gastric analyses, sedimentation rates, and blood chemistries (urea nitrogen, sugar, uric acid, creatinine, calcium, phosphorus, alkaline phosphatase, cholesterol, cholesterol esters, total protein, A/G ratio). The only changes noted were in the peripheral blood picture in practically every case and in the myelogram in one case (Case 48) (total nucleated bone marrow counts were not done). In the later cases, only the blood picture was followed routinely because of the negative results obtained in the first group.

Hodgkin's Disease: The results with Hodgkin's disease are summarized in table 1. In all cases the diagnosis was established by lymph node biopsy. Sections made elsewhere were reviewed by the pathologists of this hospital. As is apparent from the table, temporary remissions were obtained in 20 of the 24 cases studied. Of the four complete failures one died on the second day of treatment of genito-urinary hemorrhage which had begun before admission, and cannot therefore be considered an HN2 failure. There were two toxic deaths. The first one occurred as a result of agranulocytosis and

* The nitrogen mustard used in this study was supplied by Merck & Co., Rahway, N. J., on the approval of the Committee on Growth, National Research Council.

TABLE I

Hodgkin's Disease

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
1	S. P.	29	F	1940	X-ray, good response until Sept. 1946	9/27/46	0.1 mg./K×4	3 months	2 months	Lymphadenopathy became x-ray resistant. Responded to HN2 with weight gain and general symptomatic improvement.
						12/18/46	0.1 mg./K×4	2 weeks	None	Died Jan. 1947 with agranulocytosis thrombocytopenia, esophagitis, proctitis, generalized hemorrhages due to HN2 toxicity. P. M. revealed fibrosis of lymph nodes. No evidence of Hodgkin's except a single nodule in spleen. See case report.
2	F. S.	33	M	1943	X-ray, good response until 1946, but developed draining sinuses.	7/22/46	0.1 mg./K×4	8 weeks	5 weeks	Rapid disappearance of pruritus after HN2. Moderate reduction of adenopathy. Marked subjective improvement. Ulcerations smaller, drainage less.
					Became x-ray resistant early 1946.	9/27/46	0.1 mg./K×4	7 weeks	None	Much less effect from second course. Nodes slightly smaller.
					X-ray Oct. 1946—followed by increase in size of cervical nodes.	11/20/46 12/4/46 12/31/46	0.1 mg./K×4 0.1 mg./K×4 0.1 mg./K×4	6 months	5 months	No response to third course. Following fourth course, lymphadenopathy diminished, pruritus subsided, symptomatically improved. Ulcers healed but nodes increased after four weeks. After fifth course, marked decrease of nodes, diminution of pain and itching.
					X-ray from Jan. to June 1947—improvement fairly well maintained.	6/12/47	10 mg.×4 (0.15 mg./K×4)	6 months	3 months	Moderate subjective improvement, decrease of edema of arms after sixth course. HN2 burn of foot healed in one month. Persistent anemia responded to transfusion. Admitted to chronic disease hospital, where in Dec. 1947 condition was poor. See case report.

TABLE I—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
3	W. S.	41	M	1944	None	8/23/46	0.1 mg./K×4	3 months	1 month	Marked response to HN2. Pel-Ebstein fever terminated abruptly. Lymph nodes smaller, good appetite, feeling of well-being.
						12/5/46	0.1 mg./K×4	4 weeks	3 weeks	Marked improvement after second course. Mediastinal lymph nodes disappeared.
						1/7/47	0.1 mg./K×4	5 weeks	3 weeks	Moderate improvement after HN2. Temperature dropped.
						2/25/47	0.1 mg./K×2	4 weeks	3 weeks	Liver, spleen now palpable. Temperature drop after HN2 (possibly coincidental). Short course given because of low WBC and platelets.
						3/20/47	0.1 mg./K×4	4 weeks	1 week	Drop in WBC accompanied by throat ulceration followed HN2. Responded to penicillin. Nausea, vomiting relieved for only one week. No response to transfusions. Died 4/16/47. P.M. findings—generalized Hodgkin's.
4	M. S.	50	M	1937	X-ray, good response until 1944. Completely refractory in 1946.	10/11/46	0.1 mg./K×4	8 weeks	5 weeks	After HN2 marked reduction of cervical spine pain, slight relief of radicular pain of left arm. Nodes slightly smaller.
						12/11/46	0.1 mg./K×4	6 months	3–4 months	No relief of pains or decrease of nodes following HN2. Relief obtained with added radiotherapy although previously x-ray resistant.
					X-ray, March–April 1947, some improvement in ulcer. Reduction of arm edema.	6/9/47	0.1 mg./K×4	6 weeks	None	Spleen, nodes smaller, no other improvement from HN2. Patient transferred to chronic disease hospital Sept. 1947, died there Oct. 1947. P.M. findings—generalized Hodgkin's.
5	S. H.	38	M	1942	X-ray, minimal response.	Sept. 1946	0.1 mg./K×3	None	None	Died during treatment with HN2 of exsanguinating hemorrhage from urinary bladder. P. M. findings—generalized Hodgkin's.

TABLE I—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
6	A. G.	30	F	1940	X-ray 1945—moderate response. ACS injections 1946, very little response.	10/16/46	0.1 mg./K×4	2 months	6 weeks	Sister had Hodgkin's. Marked symptomatic improvement after HN2. Ascites, cough, pain disappeared. Adenopathy reduced. Edema, pleural fluid disappeared in two weeks.
						12/19/46	0.1 mg./K×4	3 months	2 months	Marked but less striking improvement after second course. Stomatitis developed with low WBC, responded well to penicillin. Readmitted in March 1947 with severe recurrence. Little response to x-ray. Refused HN2 and signed out to another hospital, where progressive downward course continued until death 9/9/47. No P.M.
7	R. S.	23	M	Oct. 1946	None	Nov. 1946	0.1 mg./K×4	10 months	>10 months	Excellent response to HN2. Dyspnea due to mediastinal adenopathy cleared. Nodes smaller. Improvement has been maintained following short course of x-ray.
8	A. G.	22	F	1943	X-ray, good response until four months before admission.	Oct. 1946	0.1 mg./K×4	2 months	>2 months	Dramatic favorable response to HN2 with almost complete disappearance of nodes, abdominal and bone pains, lung infiltration and abdominal mass. Marked increase of appetite and well-being, no longer bedridden or cachectic.
9	J. S.	31	M	1942	X-ray, minimal response.	Dec. 1946	0.1 mg./K×4	3 weeks	None	No effect of HN2 noted at time of discharge. No follow-up.
10	C. S.	27	F	1936	X-ray 1936–1946—3 courses with remissions of 5 years, 3 years, 1 year, respectively.	12/7/46	0.1 mg./K×4	3½ months	2½ months	Marked symptomatic improvement after HN2. Decrease in size of liver, spleen, nodes. Increase in weight and hemoglobin. Recurrence of bone (back and leg) pain after 2½ months.
						4/10/47	0.1 mg./K×4	5 months	2 months	Marked improvement with second course. Back pain subsided rapidly. Edema of leg cleared. X-ray resumed immediately after HN2. Anemia recurred in two months, responded to transfusions.

TABLE I—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
10	C. S.	27	F	1936	X-ray April–Sept. 1947, maintained fair remission.	Sept. 1947	0.1 mg./K×4 Teropterin 5 mg. I.M. daily.	3 months	>3 months	Moderate response of fever, leg edema to HN2. Anemia still responsive to transfusions. Admitted to chronic disease hospital Oct. 1947. Steady downward course to present (April 1948).
11	N. S.	17	F	July 1946	X-ray Sept.–Dec. 1946, minimal response.	Dec. 1946	0.1 mg./K×4	6 weeks	>6 weeks	Marked improvement in appetite and sense of well-being following HN2. Mediastinal mass and pleural effusion unchanged, but dyspnea relieved.
12	E. C.	56	F	1940	X-ray, no response since 1945.	Nov. 1946	0.1 mg./K×4	1 month	None	No response to HN2. Pulmonary infiltration and hydrothorax persisted. Died four weeks after course of HN2. No P.M.
13	M. G.	35	F	Nov. 1944	X-ray, fair response until one month before admission.	Jan. 1947	0.1 mg./K×4	3 months	1 month	Good response to HN2. Complete relief of root pain. Nodes smaller. Pain recurred after one month.
					X-ray, fair response for a few months.	April 1947	0.1 mg./K×4	6 months	1 month	Again transitory relief of pain after HN2. Recurrence treated with x-ray, with slight improvement.
						Oct. 1947	0.1 mg./K×4	6 weeks	2–3 weeks	Partial relief of pain for few weeks after third course. Nodes slightly smaller. Has recently developed fever.
14	H. R.	59	M	1945	X-ray at six month intervals with good response.	2/4/47	10 mg.×4 (0.16 mg./K×4)	3 months	2½ months	Excellent response to HN2. Fever subsided promptly. Appetite and strength increased. Nodes, liver, spleen smaller.
					No response of fever to x-ray, chemotherapy, or antibiotics.	5/20/47	0.1 mg./K×4	2 months	1 month	Excellent response again. Prompt drop in temperature, return of appetite, gain of weight and strength. Spleen no longer palpable, lymph nodes much smaller.
						7/22/47	0.1 mg./K×3 Teropterin 5 mg. I.M. daily.	2 weeks	1 week	Course shortened due to sharp drop in WBC. Fever stayed down only eight days. No other improvement. Jaundice, leg edema and ascites now present. Psychosis finally led to transfer to psychiatric hospital.

TABLE I—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
15	H. R.	40	F	July 1946	X-ray Oct. 1946, little effect on mediastinal mass. X-ray therapy to chest repeated Jan. 1947, moderate response of mass, but rapid relapse.	4/23/47	0.1 mg./K×4	6 weeks	3 weeks	Slight subjective improvement after HN2. Decrease of cervical nodes, not of mediastinal mass. No effect on chest fluid or fever. Relapse after three weeks, with progressive downward course.
16	E. B.	25	M	1945	X-ray, excellent response with many courses in 1945–1946. In 1947, progressive cord symptoms not halted by x-ray.	5/26/47	0.1 mg./K×4	3 months	3 months	Excellent response to HN2. Immediate effect after first dose, halting rapidly progressing cord symptoms, with regression of signs of cord compression. Remission maintained with x-ray.
						Sept. 1947	0.1 mg./K×4	2 months	2 months	Good response to second course. Prompt relief of bone pain. Slow subsidence of fever. Marked subjective improvement. Moderate improvement of cord signs and symptoms.
						11/19/47	0.1 mg./K×4	2 months	1 month	Moderate improvement from third course, definitely less than after previous course.
17	J. DeD.	62	M	1945	X-ray 1945–1946, moderate response of adenopathy. X-ray 1947—back pains unrelieved.	7/8/47	0.1 mg./K×4	6 weeks	None	No response to HN2. Gradual and only slight drop in temperature. No other changes, subjective or objective. Died at home about 6 to 8 weeks after HN2.

TABLE I—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
18	B. E.	22	F	Summer 1946	X-ray June 1947, increased symptoms and signs of superior vena caval obstruction, enlarging mediastinal nodes.	6/23/47	0.1 mg./K×4	10 weeks	>10 weeks	Marked response to HN2. Decrease of dyspnea after first injection. Subsidence of vena caval obstruction. Marked decrease of adenopathy. Patient asymptomatic.
19	M. H.	24	F	Feb. 1946	X-ray August 1946, decrease of liver, spleen. Oct. 1946, good response for five months. Asymptomatic until adenopathy April 1947.	6/24/47	0.1 mg./K×4	3 months	2 months	Good response to HN2. Improvement of appetite, feeling of well-being. Diminution of bone pains. Spleen and liver smaller.
						9/29/47	0.1 mg./K×4	2½ months	2 months	Fair response to second course. Weakness continued but bone pains relieved. Gain of 10 pounds in weight.
						12/8/47	0.1 mg./K×4	1 month	2 weeks	Shorter period of relief following third course. Bone pains diminished for two weeks. Response definitely less than before.
20	E. S.	23	F	1941	X-ray—moderate control of symptoms. Developed x-ray burns.	5/26/47	0.1 mg./K×4	2 months	1 month	Moderately good response to HN2. Back pain less severe, pruritus decreased. Nodes slightly smaller, left breast less indurated. Appetite better. Remission very brief.
					X-ray June 1947, very little effect.	7/28/47	0.1 mg./K×4 Teropterin 5 mg. I.M. daily.	6 weeks	4 weeks	Moderate response to second course. Itching less, nodes smaller, induration reduced. Pleural fluid unchanged. Dyspnea still moderately severe. No further treatment until readmitted in September 1947 for thoracentesis. Hydrothorax rapidly reaccumulating. Pruritus, etc., again marked.

TABLE I—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
21	H. L.	20	F	1945	X-ray 1946, disappearance of nodes, fever, recurrences controlled until last few months.	7/28/47	0.1 mg./K×4 Teropterin 5 mg. I.M. daily	10 weeks	>10 weeks	Marked symptomatic improvement after HN2. Abdominal and leg pains disappeared. Superficial and abdominal nodes much smaller. Spleen no longer palpable.
						Oct. 1947	0.1 mg./K×4 Teropterin	3 months	>3 months	Second course given prophylactically during remission. One week later developed thrombopenia with purpura, and moderate leukopenia but no infection. Symptoms subsided following transfusions. Complete symptomatic remission still maintained in January 1948.
22	H. H.	24	M	May 1947	X-ray, no response.	7/24/47	0.1 mg./K×4	7 weeks	1½ weeks	Marked improvement after HN2. Compression of bronchus by nodes relieved, pupils became equal, cough and pain reduced. Dyspnea persisted. All symptoms rapidly recurred.
						9/9/47	0.1 mg./K×4	4 weeks	None	Very slight decrease in symptoms after second course. Progressive downward course terminated in death 10/5/47. Progressive leukocytosis preterminally reached 25,000. No P.M.
23	D. S.	29	F	Feb. 1946	X-ray 1946, partial response. In 1947 became radioresistant.	9/24/47	0.1 mg./K×4	7 weeks	>7 weeks	Father died of Hodgkin's at 43. Marked response to HN2. Decrease in size of neck mass, axillary nodes, some decrease of hepatosplenomegaly. Feeling of well-being. In two weeks WBC, hemoglobin, platelets dropped sharply. No bleeding. Because of pharyngitis, penicillin given in addition to transfusion. All symptoms subsided.
24	A. F.	65	M	March 1946	None.	12/8/47	0.1 mg./K×4	4 weeks	3 weeks	Good response to HN2. Marked reduction in size of infraclavicular mass and all nodes. No further radicular pain, felt stronger. Marked drop in WBC to low of 300 with ulcerative pharyngitis and decubitus ulcers. Moderately severe anemia. Platelets low even before HN2. No bleeding. Gradual weakening. Progressive downward course. Died in January 1948, four weeks after HN2. No P.M.

thrombocytopenia with hemorrhage following two closely spaced courses of HN2; the other death, also due to agranulocytosis, occurred following a single course of HN2 in the standard dosage. Fever, malaise, lymphadenopathy, pulmonary infiltrations, cutaneous infiltrates, and hepato-splenomegaly usually improved with treatment, often dramatically within a few days of institution of a course of therapy. Remissions averaged two months in duration and appeared to be shorter-lived with repeated courses. In two patients who failed to respond to the usual course of HN2, repeated courses at one to three week intervals had striking effects on the disease (Cases 1, 2). However, in Case 1, the toxic effects of the drug proved fatal.

Cases 1 and 2 are reported at length to illustrate points of special interest.

Case 1. A 29 year old white housewife first became ill in 1940. At this time she discovered a mass in the right side of her neck which was biopsied and proved to be Hodgkin's disease. She received radiotherapy to the neck and subsequently to the chest with satisfactory improvement. In September 1946, she was readmitted because of lassitude and marked stiffness of the neck, associated with induration of the right supraclavicular area. At this time she received a course of HN2 consisting of 7.5 mg. daily for four consecutive days. Eight days after the treatment she was able to move her head freely. The leukocyte count fell to 2,000 on the thirteenth post-treatment day and then rose to normal. Her general condition improved so that she felt vigorous and strong for the first time in many years. She remained well for two months. In early December 1946, she was readmitted because of recurrent stiffness of the neck, enlargement of the right cervical glands and malaise. She had gained 12 pounds during the two months preceding re-admission.

She appeared well developed and well nourished. There was slight ptosis and exophthalmos of the right eye. The right pupil was constricted. The right supraclavicular fossa was filled with a matted mass of lymph nodes. Smaller nodes were palpable in the left side of the neck, axillae, epitrochlear and inguinal regions. Fluoroscopic examination showed some infiltration at the base of the right lower lobe.

Examination of the blood revealed, hemoglobin 67 per cent; red blood cells, 3.5M/cu. mm.; white blood cells, 6,700/cu. mm.; with 79 per cent segmented polys, 3 per cent non-segmented polys, 12 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophiles; platelets, 120,000; reticulocytes, 1.0 per cent; urine showed a faint trace of albumin; ESR, 60 mm./hour.

Treatment consisted of four doses of 7.7 mg. HN2 intravenously on successive days, by the direct syringe method. As usual, there was nausea and vomiting following each dose. Successive white blood counts on alternate post-treatment days were 3,500, 5,000, 3,700. Eight days following the first course, a second course of treatment was begun. During the first and second days of the second course, white blood counts of 1,800 and 1,950 were reported. On the first day following completion of the second course, the white blood cells were 300, on the second day 200, and the next day 100. At this time, the patient had no complaints. She was given 1,000 c.c. of whole blood. Bleeding from the gums began and she developed a small ulceration on the hard palate. The platelet count was 30,000 and the white blood cells remained at 100. Despite penicillin therapy her temperature began to rise. In an attempt to stimulate leukopoiesis she was given folic acid (pteroyl glutamic acid) and crude liver. Despite numerous transfusions the hemoglobin fell progressively. She developed jaundice, gross hematuria and melena. Shortly thereafter, her left lower quadrant became tender and rigid and a purulent discharge from the rectum was noted. Streptomycin was added to the therapy to control the putative peritonitis; however, her condition continued to deteriorate. On the eleventh day following the second course of HN2, the patient died.

Postmortem examination revealed a small Hodgkin's granuloma in the spleen. There was no visible involvement of the lymph nodes. There was a diffuse necrotizing esophagitis and proctitis. Hemorrhages were prominent in the kidneys, peritoneum, pericardium, gastrointestinal tract, endometrium, lungs and skin. The liver showed only slight fatty changes and congestion.

Comment: This case indicates that nitrogen mustard is a potent therapeutic agent in Hodgkin's disease and in adequate dosage may even be curative. However, the curative dose appears to be as destructive to the bone marrow as it is to the granuloma, so that no margin of safety exists. It also illustrates the danger of repeating a course of nitrogen mustard therapy before recovery of the bone marrow. The added insult of a second course when the maximum myelotoxic effect of the first (usually 11 to 15 days following treatment) had not yet been reached, resulted in lethal depression of the bone marrow.

Case 2. A 32 year old German accountant was first admitted to The Mount Sinai Hospital June 1946. The patient had been well until August 1943, when he noted increasing fatigue, weakness and loss of weight. On examination a small firm lymph node was found in the left supraclavicular fossa. Biopsy of the node at another hospital revealed Hodgkin's disease. He was then treated with radiotherapy which was effective until 1945, when radiation no longer controlled the disease.

Toward the end of 1945, following radiotherapy, a gland in the right supraclavicular region became fluctuant and spontaneously drained thick yellow pus. Soon after, several glands in the left axilla broke down and began to drain similar material. In addition, he developed pruritic red areas on his extremities and back.

Physical examination revealed a well developed, fairly well nourished white male. There were large matted supraclavicular and cervical nodes. The inguinal, axillary and epitrochlear lymph nodes were bilaterally enlarged. Purulent wounds were noted in the left axilla and right supraclavicular area. Fluctuant masses were located in the left axilla, over the upper thoracic vertebrae, and over the left scapula. The skin of his extremities was covered with numerous circumscribed brown macular lesions. The spleen and liver were not palpable. Ptosis of the right eyelid was present and the right pupil was smaller than the left.

Examination of the blood showed hemoglobin 64 per cent, white blood cells 15,200 with a normal differential count. Roentgen-ray of the chest showed widening of the superior mediastinum. The sedimentation rate was 135 mm./hour. The tuberculin test in concentrations up to 1:100 was negative.

Aspiration of the mass in the left axilla revealed purulent material which was found to be negative for acid fast organisms or fungi. Guinea pig inoculations were negative for tuberculosis. A chronic sinus tract formed following aspiration.

Treatment consisted of a course of sodium arsenite subcutaneously. He received a total of 0.74 gram as a 2 per cent solution over a period of 30 days. During this period there was increasing weakness and anorexia. The hemoglobin fell to 40 per cent and he developed a leukopenia of 4,200. On July 23, 1946, the patient was started on his first course of HN2. He was given 0.1 mg. per kilogram of body weight daily on four consecutive days. By the completion of the course, he experienced disappearance of pruritus. He felt subjectively much improved. There was moderate reduction of the lymphadenopathy and the ulcerations became smaller with diminished drainage. He returned two months later because of recurrence of the original complaints plus pronounced submental adenopathy. A second course of HN2 was begun on September 27, 1946. The effect of therapy was much less dramatic than from the previous course. The submental gland was slightly reduced in size, but the pruritus remained unchanged.

The patient was readmitted two months later because of pains in the back and enlargement of the submental glands. He had received radiotherapy to these areas with no effect in the interval. Pruritus remained unchanged. There was no increased weakness or loss of weight since the last admission. The lower portion of his face was red and swollen. The submental nodes were stony-hard and quite large, and there was a cervical kyphosis. The remainder of the physical examination was essentially the same as at the time of first admission. The hemoglobin was 75 per cent; red blood cells 4.1M/cu. mm.; white blood cells 9,800/cu. mm. with segmented neutrophiles 70 per cent, non-segmented neutrophiles 12 per cent, lymphocytes 14 per cent, monocytes 4 per cent; platelets 120,000; reticulocytes 1 per cent.

The patient was treated with another course of HN2 0.1 mg. per kilogram daily for four days. Therapy was started on November 20, 1946. There was no remarkable improvement during the next nine days. The leukocytes fell to 4,500, the hemoglobin to 54 per cent. Although the maximum expected leukopenic effect of the HN2 was not yet reached, it was decided to administer another course, since it appeared that the normal dosage recommended was inadequate for this patient. Hence, on December 2, 1946, a fourth course of HN2 was given. Following this course marked improvement was noted: the submental glands diminished greatly in size, pruritus subsided, the pain in the cervical region disappeared, and the patient felt very much improved. On the day of the last dose his white blood cells fell to 900, but the hemoglobin and platelets were relatively normal. For the next three weeks the white cell count ranged between 400 and 1,400. During this period of marked leukopenia there was no evidence of infection. The ulcer in the right supraclavicular area healed completely and the one in the left axilla became clean and presented healthy granulation at the base. The submental glands appeared to be increasing in size again on December 31, 1946, and a fifth course of HN2 was administered. Following this therapy the submental glands again receded. The leukocytes, which had risen to 5000 per cu. mm., fell to 1,500 and the hemoglobin to 48 per cent. The patient was transfused and was discharged one week later markedly improved.

Following discharge the patient was able to return to work for the first time in two years. His remission was maintained until May 1947 with the aid of occasional roentgen-ray therapy to the submental nodes which were now again moderately radio-sensitive. In June 1947 he developed progressive weakness, anemia, increasing lymphadenopathy with edema of both arms and recurrence of the draining wounds in the right supraclavicular area and the left axilla.

He was readmitted in June 1947 for a course of HN2, 10 mg. (0.15 mg. per kg.) daily for four days. There was moderate subjective improvement following this therapy, with decrease of the edema of the arms and regression of the lymphadenopathy. The ulcerations became less purulent, but did not close. The anemia responded to transfusions. About 10 days following an injection into a dorsal vein of the foot with slight extravasation which caused brief, moderate pain, a hemorrhagic bleb 2 to 3 cm. in diameter developed at the site of injection. The bulla broke down superficially, was moderately painful, but healed within one month. Other extravasations of HN2 in this patient (due to the difficulty in finding suitable veins because of multiple thromboses and the edema of the arms) were not followed by any complications.

The remission was not sufficient to permit gainful employment. The patient was admitted to a chronic disease hospital where roentgen-ray and local therapy resulted in healing of the supraclavicular ulceration but did not improve the axillary wound. He became progressively weaker and anemic although not cachectic, and by December 1947 he was able to leave his bed only with difficulty.*

* The patient died March 1948.

Comment: This patient with Hodgkin's disease with cutaneous infiltrations which had broken down spontaneously forming chronic draining sinuses, had become resistant to radiotherapy, but responded to intensive and repeated HN2 treatment with subsidence of all symptoms and healing of the ulcerations. Remission was maintained for five months. Localized swellings due to Hodgkin's nodes were again radio-sensitive after chemotherapy. As in Case 1, the early repetition of a course of nitrogen mustard (nine days) produced marked leukopenia associated with marked improvement in the granulomata. In this case the leukopenia did not cause symptoms.

Leukemia: The results obtained in the treatment of chronic leukemia are summarized in table 2. Of the four cases of lymphatic leukemia, three responded with diminution in lymphadenopathy and hepatosplenomegaly and with subjective improvement but with relatively little change in the blood picture. One patient with lymphosarcoma which had progressed terminally to lymphatic leukemia failed to respond to therapy. The two patients with chronic myelogenous leukemia obtained no improvement. Case 26 is of particular interest because of the development of lymphatic leukemia in a patient who had been demonstrated to suffer from Hodgkin's disease eight years earlier. With the onset of the leukemia the lymphadenopathy and splenomegaly became radio-resistant and progressive severe anemia developed. The response to HN2 was fair, but short-lived, characterized by reduction in hepatosplenomegaly and lymphadenopathy. The hematological picture was not benefited and relapse was prompt.

Carcinoma: Fifteen cases of carcinoma were treated with HN2. The cases are summarized in table 3. Only in Cases 35 and 43 did any objective improvement occur. In Case 35 (bronchogenic carcinoma), the metastatic supraclavicular nodes decreased in size and the clouded sensorium cleared. However, death occurred four weeks after treatment, of hemoptysis. Case 43 (Wilms' tumor), showed fleeting regression of the pulmonary metastases.

Lymphosarcoma: The eight cases of lymphosarcoma are summarized in table 4. In six cases, brief remissions characterized by reduction in lymphadenopathy were obtained. The remissions averaged four weeks, excluding Case 47 which is reported at length because of the unusually long remission.

Case 47. A 58 year old white female had noted swelling of the neck five years before admission. A biopsy of a cervical lymph node performed two years later was interpreted as lymphosarcoma. At that time she had developed nodules in the scalp, inguinal, axillary, and mediastinal lymphadenopathy in addition to the cervical involvement. She received roentgen therapy to all of these areas with rapid regression of the nodes.

In December 1946, she was admitted because of a persistent non-productive cough, dyspnea, sweating, weakness, and loss of 10 pounds. Two weeks before admission she had received two roentgen-ray treatments to the mediastinum without apparent improvement. The positive physical findings were enlarged nodes at the angle of the left jaw, multiple, bean-sized nodules fixed to the skin of the scalp, liver enlarged to four fingers'-breadth below the costal margin, spleen palpable one finger's-breadth below the costal margin, enlargement of the right axillary and inguinal nodes.

TABLE II

Chronic Leukemias

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
25	L. S.	66	M	1946	X-ray, no response. Stilbamidine, no response.	Sept. 1946	0.1 mg./K×4	1 week	None	Lymphosarcoma with terminal lymphatic leukemia. Moribund when therapy begun. No effect from HN2. Died nine days later.
26	M. G.	50	M	1938	X-ray 1938–45, good response. 1946 little effect on adenopathy, enlarging spleen and liver.	11/19/46 12/10/46	0.1 mg./K×4 0.1 mg./K×4	7 months	2 months	Hodgkin's disease at onset, later becoming chronic lymphatic leukemia. Moderate response to HN2. Marked decrease in hepatosplenomegaly and lymphadenopathy. After two months recurrent anemia treated with varying success by transfusions; edema due to hypoproteinemia. Transferred to chronic disease hospital July 1947, discharged from there in September improved. December 1947 improvement maintained with periodic transfusions.
27	J. G.	47	M	1945	X-ray, one course with moderate response.	Dec. 1946	10 mg. ×4 (.13 mg./Kg.)	9 months	3 months	Chronic lymphatic leukemia. Moderate improvement after HN2. Decrease of lymphadenopathy. Increase of appetite, well-being. WBC unchanged, slight drop in lymphocytosis. Died August 1947, at home.
28	B. G.	38	F	1944	X-ray, moderate response 1944–47. No effect in 1947. Urethane P.O. and I.V. no effect 1947. Radioactive P, no effect in 1947.	7/28/47	0.1 mg./K×4 Teropterin 5 mg. I.M. daily	1 week	None	Advanced chronic myelogenous leukemia. No response of clinical course or WBC to HN2. Transferred to chronic disease hospital August 1947. Died there in November 1947. P.M. showed leukemia.

TABLE II—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
29	N. D.	38	F	Aug. 1945	X-ray 1945 and 1946, good but very temporary response. Urethane Nov. 1946, splenomegaly reduced. In 1947 no response to urethane or x-ray.	8/5/47	0.1 mg./K×4	4 weeks	1 week	Chronic lymphatic leukemia. Moderate response to HN2. Proptosis of right eye decreased. Slight decrease of size of nodes. Disappearance of papilledema O.D. with marked improvement in vision. Subjectively improved. Ascites recurred, required tapping. Died at home September 1947 approximately three weeks after discharge.
30	G. W.	43	M	1944	X-ray 1945–1946, good response. Urethane Oct. 1946, slight response. P32 1947, no noticeable effect.	9/13/47	0.1 mg./K×4	3 weeks	None	Chronic myelogenous leukemia. No response to HN2. Died at home October 1947, approximately two weeks after discharge.

TABLE III

Carcinomas

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
31	S. M.	60	M	1946	None	11/27/46 12/7/46	10 mg. ×4 10 mg. ×4 (.17 mg./Kg.)	6 weeks	None	Liver biopsy, small round cell CA probably metastatic from lung. Some relief of cough and abdominal discomfort following HN2. No other improvement. Marked leukopenia and moderate thrombopenia following second course.
32	J. DeB.	41	F	Sept. 1946	None	Jan. 1947	0.1 mg./K×4	1 month	None	Biopsy, infiltrating mature squamous cell CA of the lung. No response to HN2. Gradual downward course, ending in death 2/15/47 at chronic disease hospital. No P.M.
33	P. R.	51	M	Aug. 1946	None	Dec. 1946	0.1 mg./K×4	1 month	None	Squamous cell CA of lung, inoperable. No response to HN2.
34	P. S.	51	F	Aug. 1946	None	11/26/46 12/19/46	0.1 mg./K×4 0.1 mg./K×4	2 months	None	Squamous cell CA of lung with pleural metastases. No response of fever, effusions, masses to HN2.
35	A. L.	47	M	Oct. 1946	X-ray, no response.	Nov. 1946	0.1 mg./K×4	4 weeks	4 weeks	Bronchogenic adenocarcinoma. Supraclavicular nodes softer and smaller. Node biopsy showed necrosis after HN2. Sensorium clearer. Died at home due to hemoptysis two weeks after discharge.
36	M. E.	52	M	Jan. 1946	Lobectomy RLL, partial lobectomy RML, RUL.	Jan. 1947	0.1 mg./K×4	3 weeks	None	Adenocarcinoma of lung, metastases to nodes and skin. No response to HN2.
37	S. E.	43	F	Jan. 1945	X-ray, minimal response.	Dec. 1946	0.1 mg./K×4	2 weeks	None	Bronchogenic CA, biopsied at exploratory. No response to HN2. Died of congestive failure (rheumatic heart disease) two weeks after HN2.
38	R. W.	66	F	June 1946	None	1/5/47	0.1 mg./K×4	4 weeks	None	Bronchogenic CA—inoperable. No response to HN2.
39	M. S.	38	F	Dec. 1945	X-ray, minimal response.	Nov. 1946	0.1 mg./K×4	3 months	None	Squamous cell CA of lung. No response to HN2. Slowly deteriorating.

TABLE III—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
40	A. S.	49	F	June 1947	None	7/28/47	0.1 mg./K×4 Teropterin 5 mg. I.M. daily.	2 weeks	None	Immature squamous cell CA of lung. No response to HN2. Transferred to chronic disease hospital July 1947. Deteriorating steadily.
41	J. S.	47	F	1943	X-ray, A. C. S., no response.	10/28/46	0.1 mg./Kg. ×4	3 weeks	None	Scirrhous carcinoma of the breast with metastases to both breasts, bones, liver, peritoneum. No response to HN2. Died three weeks later. Diagnosis confirmed at P.M.
42	D. W.	4	F	1946	Nephrectomy and post operative irradiation followed by appearance of single metastasis in lung.	3/12/47	0.1 mg./K×5	3 months	None	Wilms' tumor. Metastasis to lung in February 1947. No response to HN2 or to radiotherapy. Pneumonectomy May 1947 with uneventful convalescence.
43	E. K.	2½	M	Feb. 1947	X-ray March 1947 followed by excision of kidney, appearance of pulmonary metastases.	May 1947	0.1 mg./K×4	4 weeks	1 week	Wilms' tumor. Marked resolution of pulmonary metastases after HN2, with recurrence in two weeks. Tumor nodules appeared in abdomen during and immediately following HN2.
44	R. A.	30	F	1946	Radioactive I early 1947 with no effect except decrease of mass in neck. X-ray to spine with relief of pain.	6/25/47	0.1 mg./K×4	3 weeks	None	Anaplastic metastatic CA, 1° site undetermined. No response to HN2. Transferred in deteriorating state to chronic disease hospital in July 1947.
45	J. I.	40	M	1946	None	7/18/47	0.1 mg./K×4	8 weeks	None	Metastatic melanocarcinoma. Very slight and and temporary relief of bone pains after HN2. Deteriorated steadily, died October 1947. P.M. showed generalized metastases. Primary not found.

TABLE IV

Lymphosarcoma

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
46	R. G.	55	F	Aug. 1946	X-ray—good response.	Feb. 1947	0.1 mg./K×4	5 weeks	3 weeks	Giant follicular type. Marked reduction of lymphadenopathy after HN2. Marked leukopenia and thrombopenia with increased bleeding tendency. Thrombophlebitis of leg. Lapsed into coma, died March 1947. No P.M.
47	S. J.	58	F	1944	X-ray—moderate response.	Dec. 1946	0.1 mg./K×4	12 months	11 months	Reduction of lymphadenopathy, hepatosplenomegaly and scalp nodules after HN2.
						Dec. 1947	0.1 mg./K×4	1 month	>1 month	Good response to HN2, with reduction of back pain and subjective improvement. Scalp nodules had responded to x-ray before second course. See case report.
48	L. Z.	54	F	April 1946	None	Oct. 1946	0.1 mg./K×4	6 months	2 months	Moderate symptomatic improvement with HN2 despite suppression of erythropoiesis with anemia. Relief of cough and dyspnea, reduction of mediastinal mass.
						1/6/47	10 mg.×4 (.13 mg./K)	3 months	1 month	Recurrence of signs and symptoms with eczematoid dermatitis. No response to combined radiotherapy and HN2 except for improvement in skin. Died 4/12/47 with evidence of vena caval obstruction. P.M. findings: extensive lymphosarcoma with venous obstruction.
49	F. K.	24	F	1944	X-ray 1944–1945—excellent response with complete remission for 1¼ years. 1947—no effect.	7/28/47	0.1 mg./K×4 Teropterin 5 mg. I.M. daily	4 weeks	None	Onset 1944 as chronic lymphatic leukemia. Recurrence in 1947 as giant follicular type of lymphosarcoma completely resistant to radiotherapy. Complicated by hypoproteinemia. No response to HN2. Progressive deterioration until death 8/30/47. P.M. findings: extensive lymphosarcoma with large retroperitoneal masses, infiltration of all organs.

TABLE IV—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
50	B. G.	53	M	April 1946	X-ray for one year with moderate response.	5/2/47	0.1 mg./K×4	2 months	6 weeks	Prompt excellent response to HN2 with decrease of nodes, feeling of well-being and improved appetite. Maintained improvement after discharge.
						7/11/47	0.1 mg./K×4	10 days	>10 days	Moderate response to HN2. Marked decrease in bone pain, gradual decrease of edema, less change in size of nodes. Discharged to V. A. hospital for chronic care.
51	E. H.	63	F	April 1947	None	8/12/47	0.1 mg./K×4 Teropterin 5 mg. I.M. daily.	4 weeks	1 week	Fair response to HN2. Abdominal mass no longer felt. Axillary node smaller. Slight brief subjective improvement. Progressive deterioration until death in September 1947. No P.M.
52	S. H.	53	F	Nov. 1946	None	2/19/47	0.1 mg./K×4	6 months	2 weeks	Good response to HN2. Nodes much smaller. Recurrence of weakness, nausea, vomiting, fever treated by x-ray with excellent response in May 1947. Since then, remained fairly well. Last seen in August 1947, with improvement maintained.
53	G. H.	67	M	Dec. 1943	X-ray 1944, moderate response. Paracentesis for chylous ascites with no recurrence. X-ray 1947, little effect.	10/22/47	0.1 mg./K×4	10 weeks	None	No effect of HN2. Chylous pleural fluid and ascites reaccumulated. WBC and platelets remained at low figure of pretreatment levels. Edema, weakness, anemia persisted. Bedridden at home, gradually deteriorating in January 1948.

fading ecchymoses on the lower legs. Chest roentgenogram revealed a large mediastinal mass. The blood picture revealed hemoglobin 51 per cent, white blood cells 3,150, platelets 20,000. She was treated with a course of four injections of HN2, 0.1 mg. per kilogram, with rapid, well-marked shrinkage of the axillary nodes, liver, mediastinal mass and scalp nodules. The leukopenia and thrombocytopenia were not aggravated by therapy during the two week period of hospital observation.

During the next 10 months she regained her appetite, weight and strength. In October 1947 she began to complain of back pain, for which she received one roentgen-ray treatment without effect. During the next two months she developed intermittent fever, sweating, anorexia, weakness, and mild cough. She was readmitted in November 1947 for a second course of HN2. Physical examination disclosed an egg-sized node at the angle of the left jaw, tenderness in both upper quadrants, liver and spleen each 3 fingers'-breadth below the costal margin, a firm grapefruit sized mass in the mid-lower abdomen, and inguinal adenopathy. There were marked varicosities of the legs with moderate edema. Tenderness was elicited over the twelfth dorsal vertebra. Hemoglobin was 75 per cent, white blood cells 6,350/cu. mm., platelets 180,000. The scalp nodules had recurred, but had disappeared again following roentgen-ray irradiation.

A second course of HN2 was administered with improvement in appetite, subsidence of back pain, diminution in size of lymph nodes and slight decrease in the size of the mediastinal mass. During the one month period of observation the abdominal findings did not change significantly.

Comment: The 10 month period of remission following the first course of HN2 represents an unusually favorable response in this disease.

Miscellaneous: Table 5 summarizes 11 cases of miscellaneous diseases. Of the three cases of reticulum cell sarcoma, one (Case 58) responded to HN2 therapy with a prolonged remission (still maintained at end of five month observation period) characterized by reduction of hepatosplenomegaly, subsidence of fever and icterus. The other two patients (Cases 59, 60) experienced exceedingly brief improvement. One patient with widespread spindle cell sarcoma of the bones (Case 57) and one with Boeck's sarcoid (Case 62) were not benefited by HN2. Two patients with undiagnosed tumors, thought to be mediastinal (Case 64) and retroperitoneal (Case 63) lymphomata were treated. The former experienced marked relief of venous and bronchial obstruction. The latter was briefly relieved of abdominal pain associated with slight reduction in the size of the mass. One patient (Case 56) with lymphosarcoma proved by inguinal lymph node dissection in 1941, developed generalized lymphadenopathy, fever, and splenomegaly in 1946. He received roentgen-ray therapy and then HN2 without benefit. Postmortem examination revealed miliary tuberculosis without evidence of lymphosarcoma. The impression was that surgical dissection had eradicated the localized lymphosarcoma and that the subsequent tuberculosis, which mimicked generalized lymphosarcoma, was not responsive to HN2.

Of the two cases of mycosis fungoides, one (Case 55) responded with marked objective and subjective improvement after one course of 10 mg. (0.17 mg. per kilogram) HN2 daily for four days. The improvement of the skin lesions and the reduction of lymphadenopathy and splenomegaly

TABLE V

Miscellaneous Diseases

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
54	S. M.	74	F	1941	Local therapy, no effect.	2/16/47	0.1 mg./K×4	1 month	None	Mycosis fungoides. No response to HN2. Slight relief of itching for only one week. No effect on skin lesions.
55	H. G.	55	F	1941	Local therapy—no effect. X-ray—partial control over three years up to last five months.	1/6/47	10 mg.×4 (.17 mg./Kg.)	5½ months	3 months	Mycosis fungoides. Moderate response to HN2. Definite improvement of skin lesions with disappearance of nodules, reduction of erythema and induration, of lymphadenopathy, and of splenomegaly. Partial relief of itching. Returned to hospital 4/23/47, with exacerbation of skin lesions and infiltration in mouth. Radiotherapy with good response.
56	M. M.	24	M	1941 1946	X-ray 1941 for inguinal adenopathy (lymphosarcoma diagnosed by biopsy)—nodes disappeared. X-ray 1946–47 for recurrence involving prostate, seminal vesicles, axilla—no effect.	1/7/47	10 mg.×4 (.16 mg./Kg.)	6 weeks	None	Lymphosarcoma proved by inguinal node biopsy in 1941. Treated with x-ray. Recurrent adenopathy, rectal masses, splenomegaly in 1946 not responsive to x-ray or HN2. Transient purpura and thrombopenia followed course of HN2. Patient died Feb. 1947. P.M. findings: caseous tuberculosis with hematogenous dissemination. No evidence of lymphosarcoma.
57	F. F.	38	F	1945	X-ray early 1947—minimal relief of bone pains.	5/14/47	0.1 mg./K×4	4 weeks	None	Pleomorphous spindle cell sarcoma of bone, rapidly growing. No response to HN2 or x-ray. Died soon after treatment. P.M. findings: Spindle cell sarcoma of bones and hilar nodes and SBE on rheumatic valves.

TABLE V—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
58	L. S.	49	F	1946	X-ray—no effect.	March 1947	0.05 mg./K×2 0.1 mg./K×3	5 months	>5 months	Reticulum cell sarcoma. Half dose given because of leukopenia before treatment. Hepatosplenomegaly, icterus, fever subsided. WBC unchanged. Still well in August 1947.
59	M. F.	56	M	1947	None	August 1947	0.1 mg./K×4	1 week	None	Reticulum cell sarcoma. Remission of fever for three days. Spleen shrunk from five fingers below costal margin to costal margin. Died one week after treatment. P.M. findings: reticulum cell sarcoma involving both adrenals.
60	F. T.	42	M	July 1947	X-ray August 1947 —partial but very temporary response.	11/17/47	10 mg.×4 (.15 mg./K)	5 weeks	One week	Reticulum cell sarcoma, rapidly growing. Slight temporary response to HN2. Neck mass decreased in size for one week. Recurrence together with dorsolumbar back pain partly controlled by x-ray therapy.
61	L. K.	42	F	1938	None	Oct. 1946	0.1 mg./K×4	15 months	8 months	Non-leukemic myelosis. Very good response to HN2. Splenomegaly considerably reduced. Hepatomegaly slightly diminished. Hematological picture returned to normal, but rose gradually during succeeding 15 months. Splenomegaly returned to pretreatment level 15 months after therapy. See case report.
62	J. W.	39	M	1946	None	12/2/47	0.1 mg./K×4	2 weeks	None	Boeck's sarcoid. Diagnosis based on clinical and x-ray picture, and positive sarcoid skin test. No objective changes after HN2, but subjectively dyspnea was less.

TABLE V—*Continued*

No.	Case	Age	Sex	Date of Onset	Previous Treatment Results	Courses of HN2		Post HN2 Period of		Comments
						Date	Dosage	Observation	Remission	
63	H. K.	52	M	1947	None	April 1947	0.1 mg./K×4	3½ months	3 months	Lymphoblastoma—no biopsy possible at time of exploratory which demonstrated retroperitoneal mass. General though incomplete improvement following HN2. Able to work. Abdominal mass remained palpable.
						8/16/47	0.1 mg./K×4	4 weeks	1 week	Recurrent pain in RUQ relieved promptly by HN2. Liver and LUQ mass decreased moderately in size. Fever, anorexia, dyspnea occurred 2½ weeks after HN2.
						9/21/47	0.1 mg./K×4	1 month	None	Severe anorexia, weakness, anemia, with melena. Progressive downward course unaffected by HN2. Died one month later. No P.M.
64	H. D.	52	M	Sept. 1947	X-ray 1947—no improvement.	10/27/47	0.1 mg./K×4	4 weeks	2 weeks	Diff. diagnosis between bronchogenic carcinoma and lymphoma cannot be made. Excellent response to HN2. Able to lie flat for first time since onset. Superior vena caval obstruction and edema cleared but all recurred in two weeks. Chylothorax persisted.
						12/3/47	0.1 mg./K×4	2 weeks	>2 weeks	Dyspnea and orthopnea cleared again, after HN2.

were maintained for three months. The other patient failed to respond to 0.1 mg. per kilogram daily for four days.

The one patient with non-leukemic myelosis (Case 61) is reported at length.

Case 61. A 42 year old white female was admitted to the hospital on September 28, 1946. Eight years prior to her admission the patient had noticed a large area of ecchymosis over the right leg which was apparently unrelated to trauma. Since that time she had suffered spontaneous ecchymoses over various parts of the body which slowly disappeared without symptoms. For the past six years she noted progressive enlargement of her abdomen and experienced gradually increasing fatigability.

The morning of the day of admission she suddenly developed agonizing, sharp pain in her right upper quadrant which radiated to the back and which was associated with a feeling of faintness. No abnormal genito-urinary history could be elicited.

Physical examination at the time of admission revealed a well developed and well nourished adult female in no acute distress. The skin showed an area of fading purpura over the left thigh with fine varicosities in this region. There were areas of increased pigmentation over the sternum and over the ankles. The abdomen was protuberant and the liver was enlarged to three fingers below the right costal margin. It felt smooth and firm. The spleen filled the left half of the abdomen reaching down to the iliac crest and was firm, smooth and non-tender. The rest of the physical examination was normal.

On admission her hemoglobin was found to be 70 per cent; white blood cell count 26,000, with 73 per cent polymorphonuclear cells, 18 per cent stabs, 5 per cent lymphocytes, 1 per cent basophiles and 3 per cent myelocytes. The platelet count was 320,000. The urine showed 1 plus albumin, 3 to 4 white blood cells and an occasional red blood cell per high power field. Sedimentation rate was 17 mm. in one hour. Stool guaiac was negative, phenolsulphonephthalein excretion 55 per cent in 2 hours, uric acid 10.8 mg./100 c.c., and other blood chemistries were within normal limits. Prothrombin index was 100 per cent of normal; urine culture was negative; hematocrit 40 per cent; blood volume 88 c.c. per kilogram. Retrograde pyelography revealed no abnormalities. Esophagogram and chest roentgen-ray were negative. Examination of the long bones was reported as showing changes in the upper ends of the femora, tibiae, and humeri, suggestive of myelofibrosis. The sternal myelogram was normal.

Investigation of the cause of her acute pain prior to admission was without results. Because the enlarged spleen was mechanically symptomatic it was decided to try HN2 therapy, although the disease was considered to be non-leukemic. For four successive mornings the patient received 5.8 mg. (0.1 mg. per kilogram) of HN2 intravenously. Following the first injection she became severely nauseated and vomited over a period of four hours, but the other three injections were not followed by nausea or vomiting. Three days after the last injection the white blood count had fallen to 14,500 and the next day the count was 8,500 with no myeloblasts nor myelocytes seen in the peripheral smear. The count continued to fall to a low of 2,000 on the twelfth day after treatment, associated with a fall in the percentage of neutrophiles from 84 per cent to 60 per cent and a rise in the lymphocytes from 4 per cent to 19 per cent. Subsequently, the white blood count rose to normal; the neutrophiles increased to 71 per cent and the lymphocytes fell to 10 per cent. At the time of discharge, three weeks after treatment the white count was 7,900 with no myeloblasts or myelocytes in the peripheral blood. The change in size of the spleen was no less dramatic. On the day following her last injection there was noted a slight but definite diminution in its size. The patient too, remarked that her abdomen felt smaller and lighter to her. The spleen continued to shrink rapidly in size for

about two weeks at which time it was about one-half its previous size. Study of the bone marrow, one week after treatment, revealed no significant changes from that prior to treatment. Concomitant with the reduction in the size of the spleen there was marked symptomatic improvement noted by the patient. She no longer was aware of her enlarged abdomen nor dragging sensation, and her strength and endurance increased. When seen six months later, there had been no change in the size of the liver (four fingers'-breadth below the costal margin) and the spleen had remained at about half its pre-treatment size. Her appetite was good and there had occurred an eight pound gain in weight associated with a persistent feeling of well-being. The blood revealed hemoglobin 78 per cent, red blood cells 4.0M/cu. mm.; white blood cells 12,200/cu. mm. with segmented neutrophiles 78 per cent, stabs 15 per cent, lymphocytes 5 per cent, monocytes 1 per cent, eosinophiles 1 per cent. Nine months after treatment, she experienced a second episode of right upper quadrant pain, which subsided spontaneously after one day, as on the first admission. At this time, her spleen was noted to be slowly enlarging. The white blood cell count was 15,000/cu. mm. She was last seen in January 1948. At that time she was steadily employed and had no complaints. However, the spleen had returned to approximately pre-treatment size. The hemoglobin was 59 per cent, red blood cells 3.8M/cu. mm., white blood cells 15,000/cu. mm. with 1 per cent metamyelocytes, 28 per cent non-segmented polymorphonuclear neutrophiles, 59 per cent polymorphonuclear neutrophiles, 7 per cent lymphocytes, 4 per cent monocytes, 1 per cent basophiles, 3 per cent eosinophiles, 1 normoblast/100 white blood cells, 180,000 platelets.

Comment: This patient with chronic non-leukemic myelosis (myelofibrosis) with marked splenomegaly responded to HN2 therapy with dramatic decrease in the splenomegaly and with return of the blood picture to normal. Remission was maintained for seven months. However, during the next eight months, the spleen returned to its pre-treatment size and moderate leukocytosis recurred.

Discussion

Our results are in general agreement with those of other investigators. Favorable results comparable to those obtained with radiotherapy followed the HN2 treatment of most cases of Hodgkin's disease. Fever, when present, subsided dramatically by the third day of therapy. A sense of well-being and regression of the lymphadenopathy were usually noted during the first post-treatment week, while the hepato-splenomegaly receded during the second week. Marked reduction in the size of the spleen, contrary to earlier reports, was common. In a few cases (Cases 4, 10, 16, 20) the pain due to bone lesions responded satisfactorily. One patient (Case 2), who had become roentgen-ray resistant, responded to nitrogen mustard and was subsequently sensitive to radiotherapy again. Relapses occurred in all cases in a few days to 10 months. In most cases, remissions became progressively shorter with successive courses of HN2. Chronic lymphatic leukemia, lymphosarcoma, mycosis fungoides and reticulum cell sarcoma showed variable responses. Carcinomas were uniformly unresponsive except for one bronchogenic adenocarcinoma and one Wilms' tumor (Cases 35, 43). One patient with chronic non-leukemic myelosis was dramatically benefited

with diminution in the size of the spleen and restoration of the normal blood picture (Case 61).

Post-treatment biopsies usually revealed necrobiosis and necrosis; but since these are frequent findings even in untreated malignancies, their significance cannot be evaluated.

No cures were observed. However, in one patient with proved generalized Hodgkin's disease, only one small splenic granuloma with degenerative changes could be found at postmortem examination. Death in this case was due to agranulocytosis and thrombocytopenia secondary to excessive therapy. Since almost complete suppression of the granulomatous disease was obtained, this patient illustrates the desirability of treating with the maximum tolerated dosage. Furthermore, the evidence suggests that even refractory cases respond with longer remissions to closely spaced multiple courses. However, while early re-treatment appears advantageous, a second course within two weeks is definitely hazardous. At this time the maximum myelotoxic effect has not yet been attained or has only just been reached. The regenerating marrow, with its fewer, mitotically more active blasts, is apparently more sensitive to the reagent, so that a dramatic fall in the white blood count occurs on the second to fourth day of re-treatment. We have found that approximately one and one-half to two times the recommended standard dose of 0.1 mg. per kilogram produced no more frequent or severe leukopenia than the standard dose. However, we were unable to demonstrate any clear cut advantage in the larger dosage. Both dosage schedules resulted in unpredictable myelotoxic effects. A fatal outcome due to agranulocytosis was observed in a patient who received a single standard course (Case 24), whereas some patients who received larger doses showed only minimal leukopenia. It is our opinion that the recommended schedule of therapy might be advantageously revised to provide for an initial series of closely spaced courses for maximal therapeutic effect, perhaps to be followed by regularly spaced maintenance doses.

The toxic reactions noted by us were the same as those previously reported. They appear to be unrelated to the rate of injection. We fortunately had no significant extravascular infiltrations, but mild thrombophlebitis was common. Nausea and vomiting occurred in almost all cases, but was often milder with successive injections. No appreciable relief of this symptom was obtained with pyridoxine, atropine, teropterin or sedation. The numerous visceral function tests performed by us revealed no changes attributable to the HN2 therapy except for the hematopoietic response. Lymphopenia usually occurred between the third day of treatment and the second post-treatment day. Leukopenia below 3,000 developed in almost every case with the minimum white cell count on the third to twenty-fifth post-treatment day (average 11 days); infection was rare even with counts below 1,000. There were only four cases of infection (pharyngitis), all among the Hodgkin's cases. Anemia, secondary to treatment, was noted only twice (Cases 23, 48), and thrombocytopenia was noted seven

times, with bleeding in four. A significant change in the myelogram was noted only once (Case 48) characterized by marked depression in erythropoiesis associated with anemia, but total nucleated counts were not done. The hematotoxic effect was entirely unpredictable, nor was its severity related to the response of the primary disease. Teropterin had no effect in preventing the myelotoxic effect or in hastening recovery. The effect of combined Teropterin and HN2 therapy on the primary disease was indistinguishable from that of HN2 therapy alone (eight cases).

We are of the opinion that methyl bis (β-chloroethyl) amine (HN2) is of value in the treatment of Hodgkin's disease, occasionally in lymphosarcoma and mycosis fungoides, and probably in non-leukemic myelosis. It appears to be of no value in the treatment of carcinomas. We believe that in certain instances the nitrogen mustards have advantages over their physical counter-part, roentgen-ray. In cases of wide-spread or inaccessible lymphomatous lesions, where roentgen therapy is not feasible, the drug finds particular application. Fever due to lymphomata responds much more regularly and dramatically to chemotherapy. In moribund cases, the more rapid and occasionally dramatic effect of HN2 is advantageous. Constrictive lesions of the great vessels or the spinal cord often respond more rapidly to the chemical agent than to roentgen-rays. The initial swelling of tumor tissue often seen following roentgen-ray therapy has not been observed with HN2. For the treatment of readily accessible or localized lesions, we continue to regard radiotherapy as the treatment of choice. As with roentgen-ray, we have noted that response to HN2 may be used as a therapeutic test in the differential diagnosis of lymphomatous diseases (cf. therapeutic failure in Case 56 (miliary tuberculosis) and response in Case 59 (reticulum cell sarcoma at post mortem)).

Summary

1. Sixty-four patients with a variety of malignant diseases were treated with methyl bis (β-chloroethyl) amine hydrochloride.

2. Brief remissions were obtained in 20 of 24 cases of Hodgkin's disease including several who had become roentgen-ray resistant. Carcinomas were uniformly unresponsive (with two minor exceptions). Reticulum cell sarcoma and chronic lymphatic leukemia were only fleetingly benefited or failed to respond at all. One patient with chronic non-leukemic myelosis with splenomegaly and myelofibrosis improved dramatically. Lymphosarcoma and mycosis fungoides responded variably, but the results were usually poor. Chronic myelogenous leukemia did not respond.

3. Toxic effects similar to those previously described were noted.

4. The advantages and hazards of larger doses and repeated courses at short intervals are discussed.

5. The relative merits of roentgen-ray and nitrogen mustard therapy are summarized.

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THE PHYSIOLOGICAL AND BIOCHEMICAL BASIS FOR THE USE OF VITAMIN E IN CARDIO-VASCULAR DISEASE *

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Vitamin E first came to medical notice as a preservative of precarious pregnancies, whether habitual [1] or threatened abortions.[2, 3] Its rôle in the maintenance of normal gestation was later emphasized with respect to premature placental detachment [4] and non-eclamptic toxemias.[5] Certain uses in gynecology, such as in the menopause,[6, 7] in senile vulvitis [8, 9, 10] and even in male sterility,[11] were also reported. But, fundamentally, for the first 25 years of its existence it did justify the appellation of "fertility vitamin" which now seems so misleading.

That this vitamin played a much more significant rôle than this "bit part" could have been inferred even long before 1945 from the studies of Madsen, Mason, Hickman and Harris, Houchin and Mattill and others. For example, the musculature proved to be a major site of involvement in the E-deficient hamster, rabbit or guinea pig, the vascular system in the monkey, and the heart in the monkey, rabbit and cow. "The association of vitamin E with the reproductive process, therefore, is largely due to a laboratory accident, and it is almost time, 25 years later, that we broke the unfortunate linkage produced in most medical minds by those first aborting rats." [12] For vitamin E, to quote Hickman and Harris, is "the most versatile and active of all the vitamins."

Seen through the eyes of the biochemist, vitamin E plays a still larger rôle. It is even an anomaly among fat-soluble vitamins, since it "behaves as a water-soluble vitamin that requires a lipid carrier for transport." It is one of the two great stabilizers of the blood during the digestive journey." It is the balance-wheel of the oil-soluble vitamins and the unsaturated fats. It is implicated in phosphorus metabolism—and its effects extend to the utilization of oxygen and the aging of the whole animal organism." [13] It is both oxidant and anti-oxidant. Indeed a more versatile participant in the bodily mechanism could scarcely be imagined, and it is not too surprising, therefore, that drastic changes develop in many tissues and systems in the face of E-poverty.

As internists in general, and cardiologists in particular, may not be fully aware of the more relevant animal experimentation in this field, it can be briefly summarized here in order to illustrate the broad basis on which our studies now stand, and to encourage perusal of the original papers, notably Govier's.

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Madsen [14] first showed that myocardial scarring developed in rats after prolonged deprivation of vitamin E. Mason and Emmels [15] confirmed this, and observed gross cardiac enlargement in a large series of such animals coming to autopsy. The pigment found in their heart muscles seemed to be identical with that found in brown atrophy in the senile human heart. Gatz and Houchin [16] reported analogous findings in the hearts of E-deficient rabbits, an observation lately confirmed by Bragdon.[17]

Electrocardiographic changes similar to those seen in failing hearts in man have been found in E-low rats by Butturini,[18] and by Martin and Faust [19] in rats and rabbits, but not by Ensor [20] in rats. Mason and Telford [21] report that E-deficient monkey hearts showed myocardial fibrotic areas, although in the macaque vascular degenerations seemed to preponderate. Holman [22] has also done interesting work relating vitamin E to vascular lesions in dogs.

The study of Gullickson and Calverly [23] on the hearts of E-deficient cattle bids fair to become a veterinary classic. We understand that these authors possess a great wealth of unpublished material, accumulated from a study of over 10 years' duration. Fundamentally, their observations pointed clearly to E-deprivation in cattle producing death from heart failure, with electrocardiographic changes resembling those seen in myocardial damage in man, and with postmortem myocardial foci suggestive of those seen in rheumatic affections in the human.

An interesting piece of clinical work in the veterinary field was reported by Lambert.[24] Dogs and cats in undoubted heart failure were restored to good functional efficiency on the administration of vitamin E. This clinical work on dogs and cats has been widely substantiated, we might add, and some of these veterinary cases have come to our personal attention.

This extensive animal work, some of it antedating our own clinical observations, lays a strong a priori basis for the relationship of vitamin E to cardiovascular lesions in man, should humans ever be suspected of E-deficiency.

That the average American diet is often inadequate in available vitamin E has been clearly demonstrated by the careful calculations of Harris et al.[25] and by Quaife and Harris.[26] A very good exposition of how this can develop is given by Hickman [27] in a recent letter to the Lancet. It would appear that the average American industrial worker gets only from 10 to 90 per cent of his daily requirement of tocopherols. This deficiency is further aggravated by large intakes of milk, butter, white bread and root vegetables, as well as of rancid and unsaturated fats. This deficiency is at least as marked in the upper economic strata as in those less fortunate. The assimilation of vitamin E in healthy persons is less than 50 per cent, and in deficients may be much less.

Govier et al.[28] as well as Spaulding and Graham,[29] have carried out extensive studies on the enzyme systems of heart muscle. "Anoxia in heart muscle is the accepted cause of congestive failure." It is known that in states

of cardiac anoxia coenzyme I is broken down, although it is needed for the proper metabolism of lactate, the preferred substrate of heart muscle. Now alpha tocopherol both inhibits coenzyme I nucleotidase and can also inhibit succinoxidase and lactic dehydrogenase. Govier suggests that if heart muscle in congestive failure is E-deficient, as its low creatine content resembling that of other E-deficient muscles might suggest, this deficiency would permit coenzyme I nucleotidase to act in a system already anoxic and thus produce that breakdown of coenzyme I which is known to occur in such heart muscle. This breakdown of coenzyme I would seriously derange heart metabolism. It is noteworthy that digitoxin seems to prevent such breakdown of coenzyme I in E-deficient muscle, and that alphatocopherol also seems able to prevent its destruction, by inhibiting coenzyme I nucleotidase. Govier has more recently concluded, we understand, that the somewhat similar results in these enzyme systems are accomplished differently, the one substance increasing production of coenzyme I and the other retarding its destruction.

Our own observations [30-33] on the value of alpha tocopherol as a therapeutic agent in various types of cardiac and renal disease we do not propose to review here, as they are rapidly becoming too extensive for convenient summary. Our electrocardiographic studies should soon appear.[34, 35] We ought to emphasize, however, that our conclusions were originally pragmatic, not based on any of this animal work or dietary analysis, and stand or fall by themselves as clinical observations.

Vitamin E therapy in our hands is not substitution therapy, but a form of chemotherapy. This is a point that deserves emphasis. The doses we use are larger than nutritional studies would demand, but usually smaller dosage is ineffectual. We think of alpha tocopherol as a chemical compound which also happens to be a food constituent, but whose dosage level in established cardiac disease is not closely related to that coincidence. The analogy to the modern use of vitamin D is suggestive. A small dosage of E gives but little hint of what it can accomplish in massive dosage. What could be hoped for from a small and more nearly physiological dose administered over a period of years is, of course, quite a different consideration and one on which we have little evidence as yet, although it is a problem of vital importance.

Summary

The physiological and biochemical evidence supporting the use of vitamin E in cardiovascular disease is reviewed.

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HEPATITIS AMONG AMERICAN OCCUPATION TROOPS IN GERMANY: A FOLLOW-UP STUDY WITH PARTICULAR REFERENCE TO INTERIM ALCOHOL AND PHYSICAL ACTIVITY *

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The relationship of alcoholism to the development of cirrhosis of the liver has been a subject of investigation and controversy for many years.[1-8] More recently, the relation of antecedent attacks of acute infectious hepatitis to the later development of cirrhosis and the immediate progression of some cases of chronic hepatitis into cirrhosis has received attention.[9, 10, 11] Because of the obscurity of this relationship, and the suspicion that the possible hepatotoxic effect of alcohol might be enhanced in an already damaged liver, and since it has been frequently stated in the literature that alcohol may be a factor in precipitating relapses, most physicians have forbidden alcohol to their patients for some months following recovery from the acute disease. As the clinical picture of the present endemic, sporadic, but widespread hepatitis seen among American troops in Germany differs in several respects from the *epidemic* infectious hepatitis studied by Barker, Capps and Allen [12, 13] during the war in the Mediterranean, it was thought worthwhile to study the incidence of residuals in patients who had had hepatitis six months to one year before with particular reference to their alcoholic intake and physical activity in the intervening period. An opportunity to study this situation presented itself at the Hepatitis Center maintained by the Medical Department of the U. S. Army European Command in Germany. Shortly after its inception, the Hepatitis Center was forced by military necessity to discharge some patients with laboratory and clinical evidence of incomplete recovery from acute hepatitis. This provided an opportunity to study the effects of alcohol and exercise during convalescence as well as the period immediately following apparent cure. An attempt was therefore made to recall for further study all patients who had been hospitalized at the Hepatitis Center and discharged within a period of six months to one year. Observations made on these patients furnished the basis of this report, and

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appear to indicate that large amounts of alcohol or strenuous activity during the period of convalescence played no more significant a rôle in the incidence of residuals than total abstinence or a sedentary life in the *particular* group studied.

At the present time, it is impossible to distinguish on clinical grounds between the naturally occurring infectious hepatitis (IH) and homologous serum hepatitis (SH). Certain features of the hepatitis, both clinical and epidemiological, suggest that both forms are present among the American troops in Germany, with perhaps a greater number of the latter. A third possibility, that of naturally occurring infectious hepatitis (IH) being transmitted parenterally by inoculation is also suggested. For the purposes of this report, however, these etiological distinctions have had to be ignored as no precise separation is possible. As toxic hepatitis (usually due to carbon tetrachloride) is not uncommon among the American troops, every effort has been made to exclude this. Weil's disease has not been a problem among American troops in Germany, and leptospiral agglutinations and complement fixation on both acute and convalescent sera have been performed on all suspicious cases as well as in a check survey of the patients in the Hepatitis Center.* These have all been negative.

Materials and Methods

Without using criteria for selection other than their availability within the theater, soldiers who had been previously hospitalized for either infectious hepatitis or serum hepatitis and who had been discharged from the Hepatitis Center six months to one year before, were asked to return for follow-up studies.

Of the 652 patients who had been discharged during the period, 114 patients reported for this type of follow-up examination. Although the number of relapses in those patients who had returned to the United States cannot be ascertained, only two patients were readmitted to the Hepatitis Center with true relapses (manifested by either clinical and/or abnormal laboratory findings). One of these was known to be an alcoholic about 42 years old; the other was classified as a moderate drinker. Both eventually recovered. Their interval alcoholism is not known.

The group as a whole was representative in age of the soldiers of the U. S. Army of Occupation, ranging from 19 to 36, with an average age of 22.7. The character of illness sustained by these men had not been remarkable in severity. The average length of hospitalization initially had been 62.1 days. The great majority of these men had been in good physical condition prior to the acquisition of the hepatitis. Their diets had been adequate, even ample, both prior to the onset of the disease and during the

*These tests were performed in the laboratory of the late Dr. F. O. Boerner at the University of Pennsylvania Hospital.

period of hospitalization, averaging about 5,000 calories per day, and were of high protein and high carbohydrate composition. They were allowed about 50 grams of dairy fats per day while at the Hepatitis Center.

On return, these patients were hospitalized for a period of several days, during which an interim history was taken, a careful physical examination made, and a battery of liver function tests performed.

In the interim history, particular attention was paid to intercurrent disease, gastrointestinal complaints (especially right upper quadrant pain), epigastric pain, abdominal discomfort and flatulence, nausea, anorexia and weight loss. A precise inquiry was made into their physical activity and as to the actual amount of alcohol taken. The latter inquiry needed particular care by the physician, as all of the patients on discharge from the hospital had been told not to drink for a period of at least three months. Even though reassured, it is probable that many soldiers were reluctant to admit their actual alcohol consumption.

For purposes of comparison patients were classified on the basis of the amount of alcohol consumed in the interim as heavy, moderate and light drinkers, and unless specifically mentioned, drinking alcohol began shortly after discharge. As "heavy" drinkers we have classified those who consumed daily enough to fit into the group classified by Ratnoff and Patek [6] as "alcoholism," i.e., the *daily regular* consumption of one quart of wine, six glasses of beer, or six ounces of whiskey or distilled spirits. "Moderate" drinkers were those who drank an average of not much more than two ounces of distilled spirits every day, and those who drank less than two ounces of whiskey or two liters of beer, whether intermittently or regularly were classed as "light" drinkers.

Physical activity during the interim period was classified as "heavy" if the duty which the patient had actually been performing since discharged involved strenuous manual labor, heavy lifting, or truck driving. "Moderate" activity referred to such military duty as garrison guard duty where considerable walking but little heavy labor was required. "Light" physical activity included sedentary duties and the duties of flight personnel not requiring handling of cargo. In addition to his occupation, a man's athletic activities were taken into consideration. Thus a clerk who played basketball every night was classified as having had "heavy" rather than "light" activity.

On physical examination particular attention was paid to estimation of the size of the liver both by percussion and palpation, and to the presence of tenderness on palpation.[14, 15] The weight was taken for comparison with that recorded at the end of the previous hospitalization.

The following liver function tests were performed on all patients, and are listed along with what is considered at the Hepatitis Center as the upper limit of normal:

Test	Upper Limit of Normal
Cephalin-cholesterol flocculation[16]	<1 + at 24 hours <2 + at 48 hours
Thymol turbidity[17]	4 units
Total serum bilirubin[18]	<1.5 mg. per cent
One minute prompt direct bilirubin[18] as modified[19]	0.2 mg. per cent
Bromsulfalein excretion photoelectrically determined after 5 mg./kilo body weight[20]	Retention of 5 per cent after 45 minutes
Urine bilirubin	1 +
Qualitative Harrison spot test as modified[21]	
Urine urobilinogen (morning specimen)[22]	1.5 Ehrlich units/2 hours

Results

Of the 114 patients who returned, 68 had been discharged six months to one year previously without clinical or laboratory evidence of residuals of hepatitis. The vast majority had been on graded exercises before discharge culminating in a five-mile hike. The remaining patients had had what is usually considered laboratory or clinical evidence of residual hepatitis, most frequently laboratory findings of a minor nature. These two groups have been classified as "convalescent" and "presumably cured," and are dealt with separately in tables 1 and 2.

In table 1 are shown the findings on readmission of the patients discharged as "presumably cured," and in table 2 the findings on readmission of those discharged with residuals ("convalescent"). Table 3 contains the findings on the "convalescent" group both at original discharge and on readmission. Table 4 contains the readmission findings on the total group studied.

Of the 114 cases, 28 patients were classified as "heavy," 23 as "moderate" and 35 as "light" drinkers, while 26 denied the consumption of any alcohol in the interim period. Two patients could not be classified on their alcoholic intake because of inadequate information on the charts. Thirty-five patients had been engaged in "heavy" physical activity during the interim, 40 in "moderate" and 39 in "light."

Surprisingly enough, a higher percentage of the patients in the "presumably cured" group (41 per cent) returned with residuals than did the "convalescent" group (28.3 per cent) though of course the small numbers do not lend this any significance. Of the total group, 35.9 per cent had residuals on return, but as will be mentioned later, the "residuals" in the vast majority consisted of slight elevations in the thymol turbidity.

Surprisingly few (14 patients or 12 per cent) had any symptoms, and of those who did, six complained of mild indigestion, three complained of

TABLE I

Findings on 68 Patients Discharged as Presumably Cured Six Months to One Year Previously

	No.	%	Alcohol				Activity		
			Heavy	Mod.	Light	Total Abs.	Heavy	Mod.	Light
Patients discharged as presumably cured six months to one year previously	68	100	19	14	24	11	23	22	23
Patients without residuals on reëxamination	40	59	10	8	17	5	15	13	12
Patients with residuals on reëxamination	28	41	9	6	7	6	8	9	11
Residuals on 28 Patients									
Symptoms	12		5	2	2	3	5	2	5
Without other findings	5		1	1	2	1		2	3
With hepatomegaly	2		1	1			1		1
With impaired function	4		2			2	3		1
With hepatomegaly and impaired function	1		1				1		
Hepatomegaly	5		3	2			2	1	2
Without symptoms or other findings	2		1	1				1	1
With symptoms	2		1	1			1		1
With symptoms and impaired function	1		1				1		
Impaired liver function	21		10	3	5	3	9	5	7
With abnormal thymol turbidity	14		6	3	3	2	5	5	4
With abnormal cephalin cholesterol flocculation	2		2				2		
With bromsulfalein dye retention	5		2		2	1	2		3

Note: Number of patients with more than 1 residual = 10.

occasional right upper quadrant pain, four of occasional intolerance to fatty food, and one of bouts of epigastric pain. Only one of the patients with symptoms had any significant physical findings on review, and only four had laboratory evidence of liver dysfunction, namely slight elevations of the thymol turbidity test, the highest being 5.69 units. All other laboratory functional tests were within normal limits.

On physical examination, one patient was found to have a number of typical "spider" telangiectases scattered over his chest. The only other finding in this particular case was that the liver was tender and was palpable one finger's-breadth below the costal margin.

From the tables it may be seen that neither the amount of alcohol ingested nor the interim activity could be correlated with the residuals found in this group. This is true of both the convalescent and the presumably cured groups. For example, 42.8 per cent of the heavy drinkers had residuals on

TABLE II

Findings on 46 Patients Discharged with Residuals Six Months to One Year Previously

	No.	%	Alcohol				Activity		
			Heavy	Mod.	Light	Total Abs.	Heavy	Mod.	Light
No. of patients in group	46								
No. of patients without residuals on return	33	71.7	4	5	14	10	9	11	13
Patients with residuals on reëxamination	13	28.3 100%	3	5	0	5	4	7	2
Residuals									
Symptoms	3		1	1		1		2	1
Without other findings	2			1		1		2	
With hepatomegaly	0								
With impaired function	1		1						1
With hepatomegaly and impaired function	0								
Hepatomegaly		None							
Impaired liver function	11		3	3		5	4	5	2
With abnormal thymol turbidity	10		3	3		4	3	5	2
With abnormal cephalin cholesterol flocculation	1					1	1		
With bromsulfalein dye retention	0								

Number of patients with more than 1 residual = 1.

TABLE III

Comparison of Tests on 46 Patients Discharged with Residuals of Hepatitis Six Months to One Year Previously

	On Discharge						On Readmission					
	All Positive Test	Hepatomegaly	Cephalin-Chol. Flocculation	Thymol Turbidity	Bromsulfalein	Patients with More Than One Positive Finding	All Positive Test	Hepatomegaly	Cephalin-Chol. Flocculation	Thymol Turbidity	Bromsulfalein	Patients with More Than One Positive Finding
Heavy drinkers	10	1	1	4	4	0	3	0	0	3	0	0
Moderate drinkers	9	2	1	1	5	0	2	0	0	2	0	0
Light drinkers	12	1	3	2	6	1	2	0	0	2	0	0
Total abstainers	16	2	0	6	8	0	6	0	0	6	0	0
Total number	47	6	5	13	23	1	13	0	0	13	0	0
Heavy workers	14	2	2	4	6	0	4	0	0	4	0	0
Moderate workers	16	2	0	6	8	1	6	0	0	6	0	0
Light workers	17	2	3	3	9	0	3	0	0	3	0	0
Total number	47	6	5	13	23	1	13	0	0	13	0	0

Number of patients with more than 1 residual abnormality = 1.

TABLE IV

Comparison of Residuals in "Presumably Cured" Group (63 Patients) and "Convalescent" Group (46 Patients) with Reference to Alcohol and Activity

	"Presumably Cured"		"Convalescent"		Totals	
	No. of Patients	% of Group	No. of Patients	% of Group	No. of Patients	%
Alcohol						
Heavy	9	13.2	3	6.6	12	10.5
Moderate	6	8.8	5	10.8	11	9.6
Light	7	10.2	0		7	6.2
Total abstainers	6	8.8	5	10.8	11	9.6
	28	41.0	13	28.2	41	35.9
Activity						
Heavy	8	11.7	4	8.7	12	10.5
Moderate	9	13.2	7	15.2	16	14.1
Light	11	16.1	2	4.3	13	11.3
	28	41.0	13	28.2	41	35.9

Total number of residuals in "Presumably Cured" Group = 28 (41.0%).
Total number of residuals in "Convalescent" Group = 13 (28.2%).

return, but those who did not drink anything had residuals in 42.3 per cent of their number.

	No. Patients in Group	No. with Residuals	%
Alcohol			
Heavy	28	12	42.8
Moderate	23	11	47.9
Light	35	7	20.0
Total abstainers	26	11	42.3
Activity			
Heavy	35	12	34.3
Moderate	40	16	40.0
Light	39	13	33.4

The light drinkers had fewer residuals than any of the other groups, including the total abstainers, but this is probably not significant.

Of the six patients who had had a palpable liver at the time of discharge none had palpable livers on return. The activities of these six and their alcohol consumption were as follows:

Patient	Time Interval Since Discharge	Interval Activity	Alcohol
21340	11 months	Moderate	Heavy
21615	7 months	Moderate	Heavy
21653	10 months	Light	Light
21718	9 months	Heavy	Moderate
21899	8 months	Light	Moderate
23041	8 months	Moderate	Abstainer

Five subjects were found to have a palpable liver (none more than one finger's-breadth on the check-up examination). None of these had had a palpable liver at the time of discharge. The record of their interval activities and alcohol consumption is as follows:

Patient	Time Interval Since Discharge	Interval Activity	Alcohol
21426	10 months	Heavy	Heavy
21620	6 months	Moderate	Heavy
21673	9 months	Moderate	Moderate
22460	8 months	Heavy	Moderate
21645	11 months	Light	Moderate

Of the laboratory tests of liver function, it might be said that in both the presumably recovered group and in the "convalescent" group (those discharged with *any* abnormal finding) most of those which were positive, or abnormal, were not significantly so.

Laboratory studies of liver function demonstrated slight increase in thymol turbidity in 23 cases. All the other tests performed were within normal limits. Four of the 23 had had an abnormal thymol test on discharge from the hospital. There were nine others with abnormal thymol turbidity on discharge who returned with normal values.

The number of patients in the total group with positive thymol turbidity tests on readmission for check-up was 24.

No.	Interim Alcohol	Units of Thymol Turbidity	
		Range	Average
9	Heavy	6.3–4.3	5.3
6	Moderate	6.0–4.3	5.1
3	Light	9.6–4.3	5.6
6	Total abstainers	7.5–4.06	4.9
24			
	Activity		
8	Heavy	7.12–4.06	5.5
10	Moderate	9.6–4.3	6.4
6	Light	7.5–4.3	5.1
24			

Of 13 patients who were discharged from the hospital with a slight elevation of the thymol turbidity test, nine returned with normal tests, and four with the test unchanged but without other abnormalities.

It is interesting to note the relatively large amounts of alcohol consumed. As any classification does not quite convey the picture, in table 5 are shown

TABLE V

Findings on Heavy Drinkers at Time of Discharge and on Follow-Up

Case No.	Time Elapsed Since Discharge	Abnormality on* Initial Discharge	Alcohol Consumption per Day		Interval Occupation	Abnormality on* 2nd Admission
			Spirits in Ounces	Beer in c.c.		
23564	6 months	TT 7.19 CCF 3/3	6– 7 whiskey	1000	Sedentary	TT 5.5
23203	7 months	TT 5.25	7– 8 cognac	3000	Moderate	TT 5.69
21619	7 months	None	7– 8 whiskey	2000	Light	TT 4.37
21615	7 months	Liver palpable 1 FB	8– 9 whiskey	1500–2000	Light	None
21620	6 months	None	6–12 whiskey	5000	Light	TT 4.37 CCF 2/2
21825	6 months	None	10–12 whiskey	1500–2000	Heavy	None
21827	8 months	None	3– 4 whiskey	3000–4000	Sedentary	None
21923	12 months	None	7 whiskey	None	Sedentary	None
21940	12 months	BSP 7%	15–20 whiskey	1500–2000 b.i.w.*	Heavy	None
21972	8 months	None	4 whiskey	3000–4000	Heavy	TT 4.4
21976	7 months	None	3– 4 whiskey	3000–4000	Light	None
22064	11 months	None	4– 5 whiskey	1500	Heavy	None
22093	11 months	None	8 whiskey	1500–2000	Heavy	None
22432	9 months	None	8– 9 whiskey	1500–2000	Heavy	None
22458	10 months	None	6 whiskey	2000	Light	BSP 5.25%
22552	12 months	None	2– 3 whiskey	5000–7000	Sedentary	None
20751	12 months	None	6– 7 whiskey	10,000	Moderate	None
20781	6 months	None	4– 5 whiskey	2000	Moderate	None
20800	8 months	None	4– 5 whiskey	4000	Heavy	None
20801	9 months	None	5– 6 whiskey	5000–6000	Heavy	TT 6.3 CCF 2/2
20886	12 months	None	8– 9 cognac	None	Heavy	TT 5.19
21340	11 months	BSP 10%	3 whiskey	3500–4000	Moderate	None
21393	6 months	BSP 10%	4– 5 whiskey	None	Moderate	TT 7.12
21427	9 months	BSP 10%	6 whiskey	1000	Light	None
21426	10 months	TT 4.6	5– 6 whiskey	2000	Heavy	TT 4.6 palp. liver
21431	7 months	None	6 whiskey	2000	Light	BSP 5.25
25583	6 months	None	5 whiskey	3000	Heavy	Mild fat intolerance

* TT—Thymol turbidity.
CCF—Cephalin cholesterol flocculation.
BSP—Bromsulfalein.
b.i.w.—Twice weekly.

the findings in those patients classified as "heavy" drinkers, both on the original and re-check admissions, together with their actual consumption of alcohol.

DISCUSSION

From these findings it appears that the patients in this series who consumed relatively large amounts of alcohol in the period of convalescence six to 12 months after acute hepatitis showed no more evidence of post-hepatitic liver damage than did those patients who consumed smaller amounts of alcohol. This appears to be true both of those discharged as "presumably cured" and those discharged with minor residuals. Though more difficult

to assay, it also appears that there was little difference between the group which had been very active physically and those who were not. These findings are somewhat at variance with those reported by Barker, Capps and Allen [12] who found that alcohol in excess could definitely provoke a relapse. Sporadic infectious hepatitis, as it was seen in Germany during the period of this study, presented several differences from the *epidemic* infectious hepatitis so well studied by Barker and his colleagues. It is important to emphasize that the findings of Barker and others referred to special conditions. It should be remembered that the troops now acquiring infectious hepatitis in Germany are well nourished and in good physical condition at the time they acquire the disease. They have also been leading a relatively nonstrenuous garrison life while those studied in the Mediterranean and in the Southwest Pacific had been subjected to the fatigue and exposure of actual warfare in addition to having been on inadequate and unappetizing field rations for a long time.

It is possible that the severity of the disease is related to the nutritional state at the time of infection as well as to possible differences in the strains of the virus. The data presented suggest that the sporadic infectious hepatitis seen in well-nourished individuals is a more benign disease as regards chronicity, residuals, and relapses than the epidemic variety occurring under the circumstances of war, and that overindulgence in alcohol or in physical activity during the recovery period in this form of the disease has little effect on its outcome.

Summary

One hundred and fourteen American soldiers were studied six months to one year after hospitalization for an attack of infectious hepatitis acquired in Germany. Of these, 46 had been discharged from the hospital with slight residual abnormalities, and 68 as presumably cured. Only slight differences were noted between the two groups on reëxamination after the interval, and there were relatively more residuals present in the group discharged as presumably cured than in those discharged with slight residuals. When reexamined with particular reference to their interim activity and alcohol, it appeared that neither of these factors played a significant rôle in the appearance of residuals in either group.

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THE NOCTURNAL GASTRIC SECRETION IN PATIENTS WITH BENIGN GASTRIC ULCER *

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Introduction

The results of studies on the nocturnal gastric secretion of normal individuals and of patients with duodenal ulcer, gastric ulcer and gastric carcinoma have been summarized in a previous publication.[1] Although the number of patients with gastric ulcer in the original series was small, the data were sufficiently constant to indicate certain trends. The series now has been increased sufficiently to permit definite conclusions. The purpose of this paper is to describe in detail the periodicity and variability of the nocturnal gastric secretion in such patients and to compare them with normal subjects and patients with duodenal ulcer. To our knowledge, a similar study has not been presented heretofore.

Methods

The methods employed and the criteria used in the selection of subjects have been described previously.[1, 2] The conditions of study were identical in all. Fifty-seven observations were obtained in 25 patients with benign gastric ulcer. Microscopic evidence of the benignity of the lesion was obtained in fourteen. The presence of a benign ulcer was definitely proved by roentgen-ray examination, gastroscopy, the clinical course, or by a combination of all three in 11 individuals. All patients were admitted to the hospital because of ulcer distress and a crater was demonstrated roentgenologically in each case.

Results

Total Night Secretion

Volume. The individual volumes of the total night secretion ranged from 133 c.c. to 1,444 c.c., averaging 600 c.c. (table 1). The volume was less than 1,000 c.c. in 86 per cent of the studies. It ranged between 300 and 800 c.c. in two-thirds (figure 1). Variations were observed not only among individuals but also in the same person on different nights. The individual variation for the group averaged 25 per cent.

Free Acidity. The free acidity (concentration of free HCl) of the total night secretion ranged from 0 to 59 clinical units, averaging 21 (table 1). It was less than 40 clinical units in 87 per cent of the studies and less than

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20 clinical units in more than 50 per cent (figure 1). Anacidity in the total night secretion was observed in 13 per cent. (Free acid was present in all cases in response to histamine stimulation.)

The free acidity varied in the same individual on different nights. It is of interest that the variation in the free acidity of the total excretion exceeded five clinical units in only 12 individuals.

Mg. Free HCl. The output of free HCl for the 12 hour period averaged 454 mg., the range being 0 to 2,713 mg. (table 1). It was less than 1,000

TABLE I

The 12-Hour Continuous Nocturnal Gastric Secretion in Patients with Benign Gastric Ulcer (8:30 p.m. to 8:30 a.m.)

Case		Volume (c.c.)	Free Acid (Cl. Units)	Total Output of HCl (Mg.)
(Age)	(Sex)			
A. P. 47	M	202 594	0 3	0 56
H. A. 47	M	861 566	12 6	366 116
A. Z. 49	M	736 719	3 5	83 120
M. C. 34	F	553 524	35 37	701 714
I. B. 57	M	1122 1014	3 11	116 423
V. L. 58	M	385 335 374	14 2 0	200 24 0
J. W. 60	M	432 531	1 5	17 105
J. M. 60	M	1018	37	1327
E. F. 63	M	547 1009 558 642 449 540	9 25 5 2 2 4	176 930 99 40 33 79
L. H. 61	M	628 638	20 20	446 461
R. M. 45	M	502 371	2 2	38 30
A. N. 66	F	415 396	24 23	326 332
C. G. 60	M	1444 1113	21 25	1127 1022

TABLE I—*Continued*

Case		Volume (c.c.)	Free Acid (Cl. Units)	Total Output of HCl (Mg.)
(Age)	(Sex)			
T. S. 78	M	133 258 295	0 0 2	0 0 18
E. S. 58	M	686 1275	21 59	536 2713
C. M. 32	F	308 706	29 29	328 746
M. M. 71	F	167 172 158	0 0 0	0 0 0
C. O. 43	M	585 440	53 50	1120 801
G. P. 43	F	500 460	21 43	388 715
W. G. 58	M	645 378	7 20	155 273
J. E. 63	M	694 1024	23 10	568 386
E. H. 58	M	549 359	14 0	277 0
J. J. 30	M	601 480	30 42	657 738
J. D. 50	M	619 844 1122	20 22 57	440 662 2331
C. H. 62	M	692 859	50 39	1257 1215

mg. in 85 per cent of the studies and below 500 mg. in approximately two-thirds; anacidity was present in 22 per cent of the latter studies; less than 200 mg. were obtained in 57 per cent. The acid output exceeded 2,000 mg. in only 2 per cent (figure 1). The individual variation for the entire group averaged 26 per cent.

Individuals secreting a small amount of acid on one night in the vast majority of instances produced a small amount on successive nights; a similar constancy existed for patients with a high secretory rate. This correlation was observed also for both the volume and free acid concentration.

THE HOURLY VARIATION IN NOCTURNAL GASTRIC SECRETION

Volume. The gastric secretion was continuous; rarely, there was a lack of gastric juice for one hour; in no instance was there an absence of secretion

for as long as two hours. The highest hourly volume was 196 c.c.; the average 50 c.c.

The *average* hourly secretion decreased gradually until 5:30 a.m.; there tended to be a gradual increase during the last quarter of the night (5:30

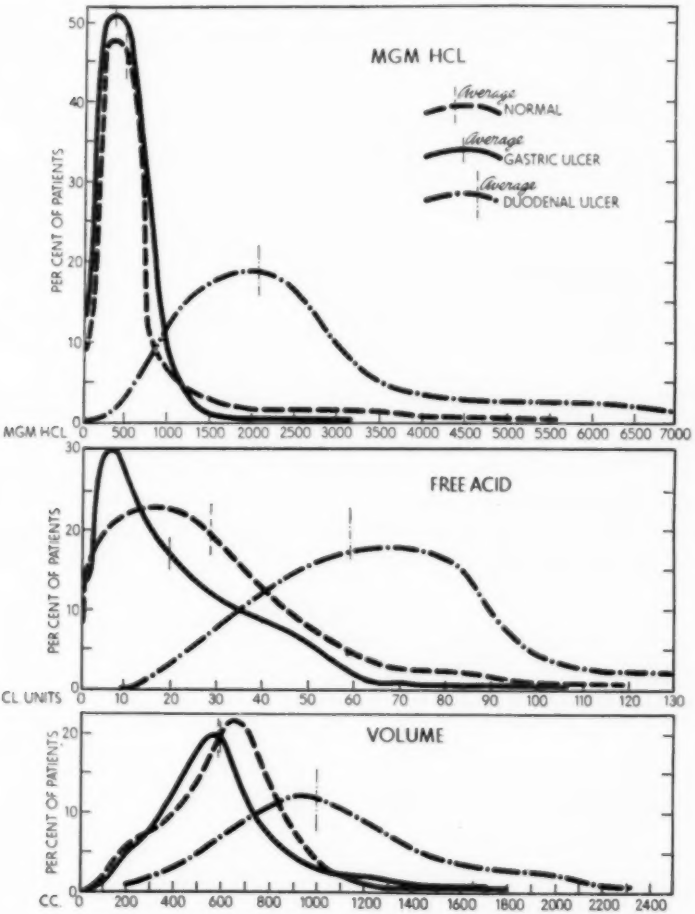

FIG. 1. Distribution curves—nocturnal gastric secretion.

a.m.–8:30 a.m.) (figure 2). The lowest output occurred between 3:30 a.m. and 5:30 a.m. The average volume was slightly greater during the first half of the night than during the last half (table 2).

There was a marked variation in the periodicity of the night secretion not only between subjects, but also in the same individual (figure 3). The rate of secretion was not constant; the fluctuations from one hour to the next were as great as 500 to 600 per cent. The hourly variation for the entire group averaged approximately 50 per cent. Four representative patterns are shown in figure 4. In this series, the maximum hourly volume occurred prior to 2:30 a.m. in all but seven of the studies.

TABLE II

The Average Volume, Free Acidity and Milligrams of Free Hydrochloric Acid Secreted During Quarterly Periods of the Night (Patients with Gastric Ulcer)

	Volume (c.c.)	Free Acidity (Cl. Units)	Hydrochloric Acid (Mg.)
8:30 p.m.–11:30 p.m.	184	29	193
11:30 p.m.– 2:30 a.m.	142	20	102
2:30 a.m.– 5:30 a.m.	114	20	82
5:30 a.m.– 8:30 a.m.	160	14	80

Free Acidity (Concentration of Acid). The secretion of acid, in contrast to the volume, was not continuous in all cases. Acid was secreted continuously throughout the night in only 19 per cent of the studies. Anacidity for two consecutive hours or more was noted in 76 per cent; in 13 per cent anacidity was present throughout the entire night. In only one subject * (M. M., table 1) did the anacidity persist on successive nights. The temporary anacidity (several hours) usually occurred after midnight.

TABLE III

The Average 12-Hour Nocturnal Gastric Secretion in Normal Individuals and in Patients with Gastric and Duodenal Ulcer

	Volume (c.c.)	Free Acid (Cl. Units)	Total Output of HCl (Mg.)
Normal	581	29	661
Gastric ulcer	600	21	454
Duodenal ulcer	1004	61	2242

The highest free acidity in one hour was 80 clinical units; the hourly value for the entire group averaged 21 clinical units. The free acidity was persistently below 50 clinical units throughout the night in 71 per cent of the studies. In no instance was it persistently greater than 50 clinical units throughout the night.

* After histamine stimulation the free acidity reached a peak of eight clinical units.

The hourly free acidity frequently equaled or exceeded that produced in response to histamine, usually among individuals with a maximum histamine response below 40 clinical units.

There was a gradual decrease in the *average* hourly concentration of acid as the night progressed (figure 2). The average free acidity was

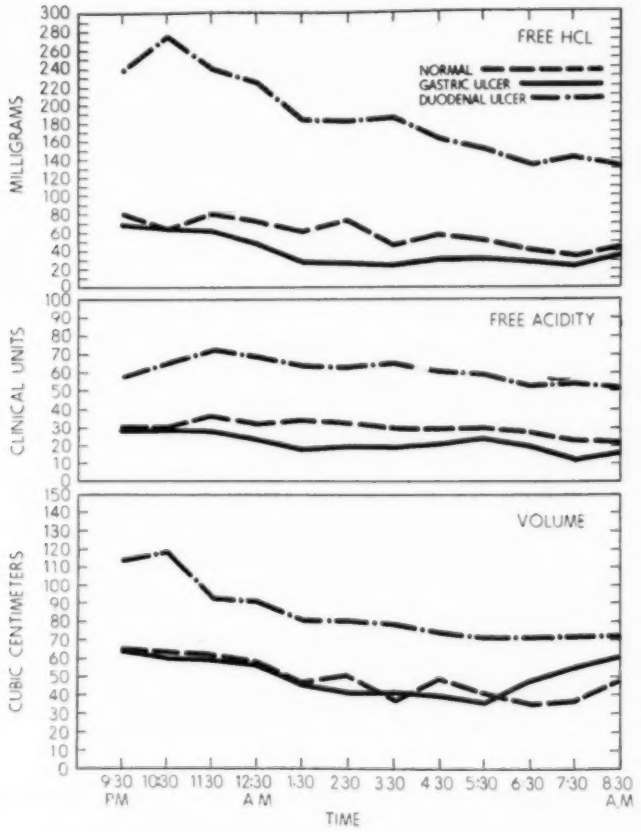

FIG. 2. Nocturnal gastric secretion—average hourly output.

greater during the first half than during the second half; the greatest decrease occurred during the last three hours (table 2).

Representative patterns are shown in figure 5. As with the volume, there was a marked variation from one individual to another. In general, the maximum concentration of acid may occur at any hour of the night. In

81 per cent of the studies it occurred before 2:30 a.m. In practically all there was a gradual decrease during the night in the same individual; however, increasing concentrations were noted in a few instances.

Varying patterns were noted in the same individual on different nights even though the conditions of study were identical (figure 3).

Milligrams of Free Hydrochloric Acid. The *average* hourly output of free hydrochloric acid gradually decreased during the night (figure 2). The amount secreted during the first half of the night was significantly greater than that during the second half (table 2), the largest decrease occurring between the hours of 11:30 p.m. and 2:30 a.m.

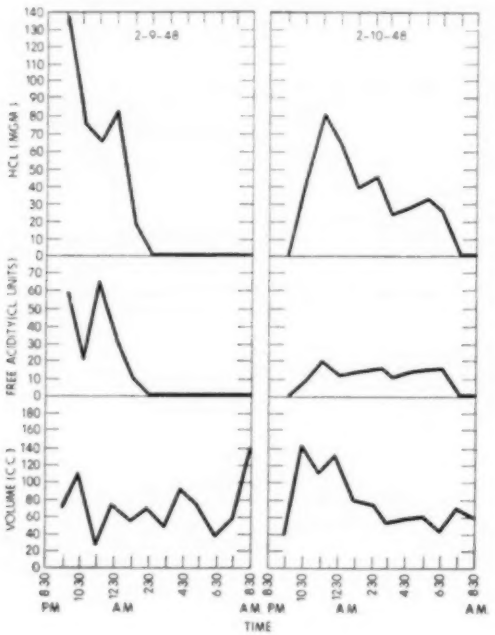

FIG. 3. Hourly variation of the volume free acidity and output of hydrochloric acid in the same individual (gastric ulcer).

The rate of secretion of acid was not constant. Rarely were similar quantities of acid secreted for two consecutive hours. Figure 4 shows the representative patterns obtained. Although the maximum hourly secretion of hydrochloric acid may occur at any time during the night, in 87 per cent it occurred prior to 2:30 a.m. A progressively increasing hourly output of acid was not observed in this series. In the few studies in which the maxi-

mum hourly secretion occurred after 2:30 a.m., the higher values were obtained during the waking hours (6:30 a.m. to 8:30 a.m.). However, in 55 per cent of the studies no free acid was obtained after 6:30 a.m. The amount of acid persistently exceeded 50 mg. throughout the night in only 2 per cent of the patients.

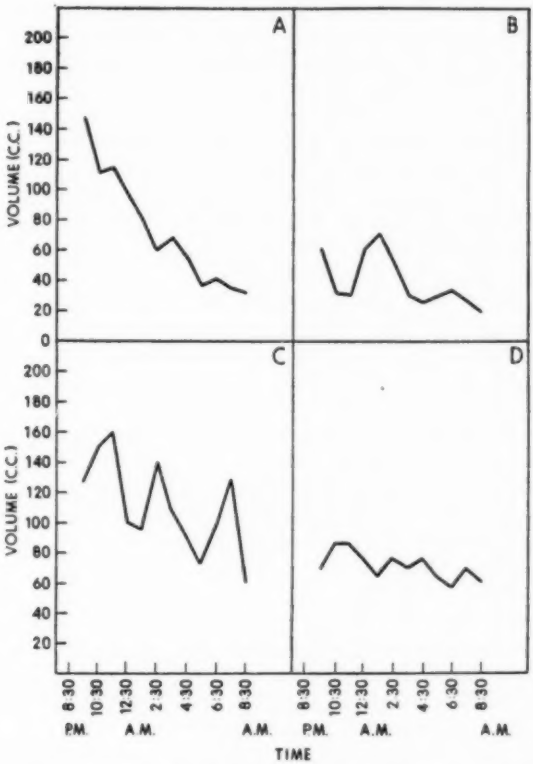

FIG. 4. Representative patterns in the hourly volume of gastric secretion during the night in patients with gastric ulcer.

The largest individual quantity of acid secreted in one hour was 470 mg.; the hourly output for the entire group averaged 38 mg.

Varying patterns were also present in the same individual on different nights (figure 3). It is of interest that the majority of individuals with long periods of anacidity during one night manifested similar periods of anacidity on successive nights.

Comparison with Normal Individuals and Patients with Duodenal Ulcer *

Volume. This study indicates that there is no significant difference in this respect between patients with benign gastric ulcer and normal individuals (table 3); the values averaging 600 c.c. and 581 c.c., respectively. The distribution curves of each practically overlap throughout (figure 1). On the other hand, the total volume in patients with duodenal ulcer, averaging 1,000 c.c. is significantly greater (table 3). In patients with duodenal ulcer the volume was less than 800 c.c. in only 32 per cent of the studies and exceeded 1,000 c.c. in 47 per cent. In patients with gastric ulcer it exceeded 1,000 c.c. in only 14 per cent (figure 1).

Gastric secretion was continuous in all three groups. In only two instances was there an absence of secretion for as long as two hours and lack of secretion for as long as one hour was exceedingly rare.

Similarly, in all subjects studied, the rate of secretion varied from hour to hour in the same individual. In duodenal ulcer patients, it was not uncommon for an individual to maintain a constantly high secretory rate for several consecutive hours (i.e. more than 75 c.c. per hour). Persistent hypersecretion was rare in normal individuals and in patients with gastric ulcer. Although there was a tendency for the average hourly secretion to decrease gradually during the night in all three groups, the secretory rate in the duodenal ulcer series consistently remained at a distinctly higher level throughout the night (figure 2).

In all three groups, in the vast majority of the subjects, the maximum hourly volume occurred prior to 2:30 a.m.

Free Acidity. The free acidity of the total night secretion varied in the three groups studied, the average being 21 clinical units in gastric ulcer, 29 in the normals and 61 clinical units in duodenal ulcer (table 3). In the gastric ulcer series it was less than 40 clinical units in 87 per cent of studies and less than 20 in 55 per cent; in no instance did it exceed 60 clinical units. In the normal group, the free acidity was less than 40 clinical units in 72 per cent of the studies and less than 20 in only 38 per cent; it exceeded 60 clinical units in 10 per cent. On the other hand, in patients with duodenal ulcer it exceeded 60 clinical units in 50 per cent of the studies; values below 40 clinical units were obtained in only 20 per cent (figure 1).

The individual fluctuations in free acid were greater in both the normal subjects and duodenal ulcer patients than in the gastric ulcer group. Variations larger than five clinical units were observed in only 12 individuals of the latter group. However, in the majority of patients with gastric or duodenal ulcer, a high concentration of acid on one night was repeated on successive nights. A similar constancy was observed in patients with low concentrations. This correlation did not necessarily hold true in normal individuals.[2]

* For complete data of normal individuals and patients with duodenal ulcer see references 1, 2 and 3.

Whereas, in patients with duodenal ulcer the secretion was continuous in all studies except three, it was not continuous in the vast majority of normal individuals and patients with gastric ulcer. Periods of anacidity for one or more hours were noted in 70 per cent of the normal studies, and in 81 per cent of the gastric ulcer group.

The concentration of acid was persistently below 50 clinical units throughout the night in 71 per cent of the gastric ulcer studies, in only

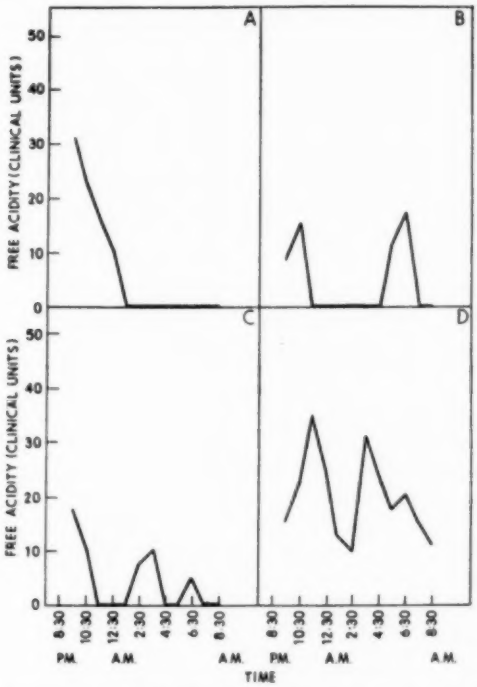

FIG. 5. Representative patterns in the hourly free acidity of the nocturnal gastric secretion in patients with gastric ulcer.

44 of the normal group and 35 per cent of the duodenal ulcer studies. On the other hand, in none of the gastric ulcer patients was it persistently greater than 50 clinical units; values higher than 50 were noted in 6 per cent of the normal group and in 35 per cent of the duodenal ulcer series.

A gradual decrease in the average hourly concentration occurred in both the duodenal and gastric ulcer groups, whereas in normal individuals it remained remarkably constant throughout the night (figure 2). However, as emphasized in a previous publication [2] composite curves are not repre-

sentative, since a high concentration in one subject is offset by a low concentration in another. Nevertheless, the average hourly concentration is highest in patients with duodenal ulcer and lowest in gastric ulcer patients.

In all three groups the maximum hourly concentration in the vast majority of instances occurred prior to 2:30 a.m. In general, the concentration gradually decreased during the night in the same individual. The

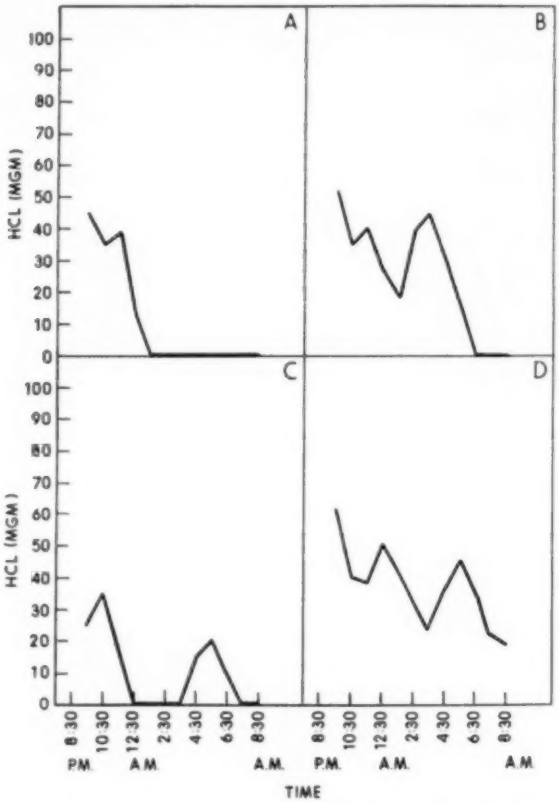

FIG. 6. Representative patterns in the hourly output of hydrochloric acid during the night in patients with gastric ulcer.

pattern varied not only from one individual to another but also in the same individual on different nights.

Mg. Free Hydrochloric Acid. The amount of free HCl for the 12 hour period was lowest in patients with gastric ulcer, the average being 454 mg.; the average for the normal group was 661 mg. and for patients with duodenal

ulcer 2,242 mg. (table 3). Although there was some overlap in the distribution, the differences are statistically significant (figure 1). In the gastric ulcer group, it was less than 1,000 mg. in 85 per cent of the studies and below 500 mg. in approximately two-thirds. Of the latter, anacidity was present in 22 per cent and less than 200 mg. were obtained in 57 per cent. In the normal individuals, the output was less than 1,000 mg. in 84 per cent of the studies and below 500 mg. in 50 per cent. Of the latter, approximately two-thirds were below 200 mg., no individual having a complete anacidity. In contrast, the output in duodenal ulcer patients exceeded 1,000 mg. in 81 per cent of the studies and 2,000 mg. in more than 50 per cent. An output less than 500 mg. was noted in only one instance.

There is a gradual decrease in the average hourly secretion of free hydrochloric acid in all three groups studied (figure 2). The hourly secretion averaged 38 mg. in gastric ulcer patients as compared with 55 mg. in normal individuals and 187 mg. in patients with duodenal ulcer. In two-thirds of the duodenal ulcer patients the output of HCl for the same hour exceeded the average output of the normal and gastric ulcer patients.

In patients with duodenal ulcer the amount was persistently greater than 50 mg. throughout the night in 63 per cent of the studies and more than 100 mg. in 32 per cent. In the normal group it was persistently greater than 50 mg. in 12 per cent and persistently greater than 100 mg. in only 4 per cent. In contrast, in only 2 per cent of the gastric ulcer patients was the hourly amount persistently greater than 50 mg. Free acid was not obtained after 6:30 a.m. in 55 per cent of the patients with gastric ulcer, in only 18 per cent of the normal group; anacidity was never observed in patients with duodenal ulcer.

The rate of secretion in the same individual was not constant in all three groups. In the majority of individuals the maximum hourly secretion of hydrochloric acid occurred prior to 2:30 a.m. Varying patterns were present from individual to individual and also in the same individual on different nights. As a rule, however, an individual with a high secretion on one night, manifested a relatively high secretion of acid in successive nights. This also held true for individuals with a relatively low secretion rate.

Comment

This study demonstrates statistically significant gastric secretory differences between patients with gastric ulcer, normal individuals and patients with duodenal ulcer. The volume of the night secretion in gastric ulcer patients is significantly lower than that of duodenal ulcer patients. On the other hand, there is no significant difference between gastric ulcer patients and normal individuals. The concentration of free hydrochloric acid and the amount of acid secreted is lowest in patients with gastric ulcer when compared with normal individuals and patients with duodenal ulcer.

No correlation existed between the amount of secretion and the location

of the ulcer in the stomach, duration of symptoms or the age of the patient. There appears to be no consistent correlation between the degree of gastritis as determined gastroscopically, with the amount of acid produced. However, the secretion is relatively lower in individuals with an associated atrophic gastritis as compared with those in whom atrophy is not demonstrated.

The explanation for the differences between the three groups remains obscure.

Conclusions

1. The secretion of gastric juice in patients with benign gastric ulcer is apparently continuous; although the secretion of hydrochloric acid is not continuous.

2. The volume of secretion and output of acid are usually higher during the first half of the night than during the last half.

3. Individual variations exist. However, patients with a low volume and secretion of acid in one night, in the majority of instances, produce a low volume and acidity on successive nights; a similar constancy exists in patients with a high secretory rate.

4. The rate of gastric secretion is not constant, varying spontaneously from hour to hour in the same individual.

5. The volume, concentration and output of acid in the fasting nocturnal gastric secretion are lower in patients with benign gastric ulcer than in patients with duodenal ulcer.

6. There is no significant difference in the average volume secreted by patients with benign gastric ulcer and normal individuals; however, the concentration of free hydrochloric acid and output of acid are lower in patients with gastric ulcer.

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CASE REPORTS

A CASE OF CHRONIC NEPHRITIS IN CHILDHOOD WITH LATER DEVELOPMENT OF SEVERE HYPERTENSION; RENAL BIOPSY *

By Earl I. Mulmed, M.D., Archie H. Baggenstoss, M.D., and Howard B. Burchell, M.D., *Rochester, Minnesota*

When physical examination reveals markedly increased arterial pressure, determination of the rôle of the kidneys in the causation of this symptom often presents a difficult problem.

The question may arise as to whether hypertension of the essential type could occur independently in a case in which evidence of past or latent chronic glomerulonephritis is found. Recently we had the opportunity of studying the histologic appearance of the kidneys and of the arterioles of the skeletal muscles in a case in which the clinical picture was that of severe essential hypertension and in which an established history of chronic glomerulonephritis in childhood was obtained. The unusual feature of the case was the discovery of vascular changes consistent with the clinical appearance of primary hypertension and the almost total absence of chronic glomerular lesions.

Case Report

The patient, a white man, 29 years of age, registered at the Mayo Clinic on May 27, 1946. His main complaint was of high blood pressure and it was his wish that sympathectomy be considered in treatment. He was an intelligent lawyer and had acquired considerable knowledge of his disease from his brother, a physician, and various internists who had treated him.

At nine years of age he had been a patient of Dr. C. Anderson Aldrich and Dr. Aldrich gave us the following facts. The patient was first examined by Dr. Aldrich in a pediatric clinic in April, 1926, when albuminuria and hematuria both graded 3 +, on a basis of 1 to 4 (in which 1 represents the mildest and 4, the most severe condition), and slight edema were noted. The blood pressure was normal and laboratory study of the blood revealed the following: nonprotein nitrogen, 96 mg. per 100 c.c. of serum; urea, 140 mg.; urea nitrogen, 70 mg.; creatinine, 1.8 mg. per 100 c.c. of blood. Gross albuminuria and hematuria continued to be present for six weeks after which the hematuria disappeared but the albuminuria, graded 2 to 4, continued to be found on approximately weekly examinations for the next year. He was seen frequently in 1927 and 1928 during which time a great deal of albumin, red blood cells (occasionally) and numerous casts were found in the urine. Similar observations were made on occasional examination of the patient in 1929 and 1930. He was examined once in the years 1930, 1932 and 1935, when albuminuria was graded 4 + but the chemical composition of the blood and blood pressure were normal. On one occasion in 1930 the blood pressure was found to be 144 mm. of mercury systolic and 72 mm., diastolic (figure 1).

* Received for publication March 24, 1947.

In 1936 when the patient was 19 years of age he was found to have hypertension during routine examination of the new students entering a university. His blood pressure was found to be 210/120. Later the average blood pressure was 180/110.

In 1936 he was thoroughly examined elsewhere and carefully maintained treatment with thiocyanate was continued for the next 10 years until approximately six months before admission. His systolic blood pressure varied between 160 and 180 mm. on this medication. The diastolic pressures during this period are unknown to us.

Six months prior to admission he began to note occasional mild frontal headaches which usually occurred one to two hours after he arose in the morning or early in the afternoon.

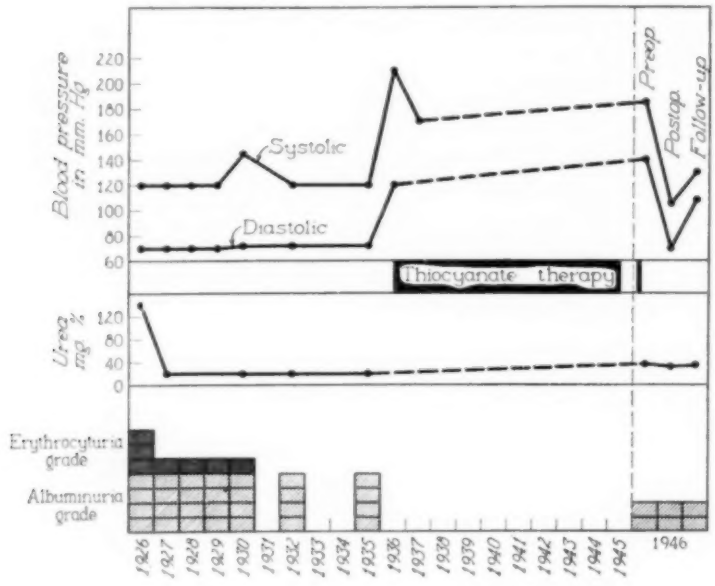

FIG. 1. Summary of findings in a 20 year period of observation.

His past history, aside from the information given herein, and family history were noncontributory.

General physical examination gave negative results except for the finding of hypertension. Clinical examination of the heart revealed that it was normal. The blood pressure was determined hourly for 24 hours; it ranged between 160 and 210 mm. systolic and 116 and 160 mm. diastolic. After administration of sodium amytal, the blood pressure dropped to as low as 150 mm. systolic and 115 mm. diastolic (figure 2). When the cold pressor test was given a rise of 28 mm. in systolic and 10 mm. in diastolic pressure occurred when the patient was in the recumbent position and when he stood no change in the systolic pressure and a rise of 12 mm. in the diastolic pressure were noted.

Examination of the fundi showed hypertensive narrowing, grade 2, with vasospastic constrictions, grade 2 to 2+, of the retinal arterioles. Minimal evidence of sclerosis was found. Cotton-wool patches were numerous and a few small flame-shaped areas of hemorrhagic material were noted in both fundi and a mixture of hemorrhagic material and exudate was observed in the left superior temporal area. Dr. Henry P. Wagener was of the opinion that the funduscopic picture was that of acute hypertensive retinopathy with little or no sclerosis and that in the presence of hypertension of this duration it was more indicative of glomerulonephritis than of primary essential hypertension.

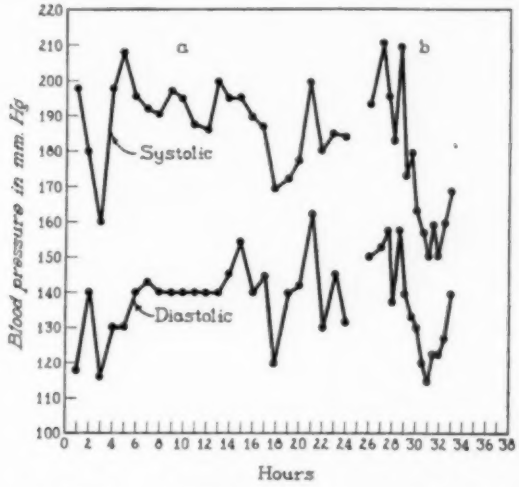

FIG. 2. Preoperative studies. (*a*) Blood pressures determined at hourly intervals for 24 hours. (*b*) Blood pressures during the amytal test.

TABLE I

Preoperative, Postoperative and Follow-Up Laboratory Findings

	Preoperative Values, June 7, 1946	Postoperative Values, July 18, 1946	Follow-up Values, October 10, 1946
Urea*	36 mg.	32 mg.	34 mg.
Creatinine*		1.2 mg.	
Sulfate†	4.6 mg.	5.1 mg.	4.8 mg.
Urea clearance‡	39.9 c.c.	139.4 c.c.	55.5 c.c.
Volume of urine per minute	1.8 c.c.	5.1 c.c.	1.53 c.c.
Sulfate clearance‡		75.9 c.c.	37.3 c.c.
Calcium†	9.8 mg.		
Phosphorus†	2.8 mg.		
Protein†	7.7 gm.		
A–G ratio	2.0/1.0		
Protein in 24 hr. urine specimen§	0.18–0.35 gm.		0.22 gm.

* Per 100 c.c. of blood.
† Per 100 c.c. of serum.
‡ Of blood per minute.
§ Per 100 c.c. of urine.

On routine urinalysis specific gravity ranged from 1.011 to 1.020, albumin was graded 2 and microscopic examination gave negative results. The urine concentration test showed that the maximal specific gravity was 1.027. The concentration of hemoglobin was 15.3 gm. per 100 c.c. of blood. The erythrocyte count was 4,980,000 per cubic millimeter and the leukocytes numbered 8,700 per cubic millimeter. Results of the flocculation test for syphilis were negative. The chemical constituents of the blood were normal and in addition the results of the urea clearance test and protein content of the urine were within normal range (table 1).

Roentgenologic examination of the thorax gave negative results and the heart was normal in size. Excretory urograms showed no evidence of small or contracted kidneys. The electrocardiographic findings were normal.

While being allowed moderate activity the patient was given potassium thiocyanate. The concentration was maintained at approximately 8 mg. per 100 c.c. of blood and his blood pressure averaged 190 mm. systolic and 130 mm. diastolic.

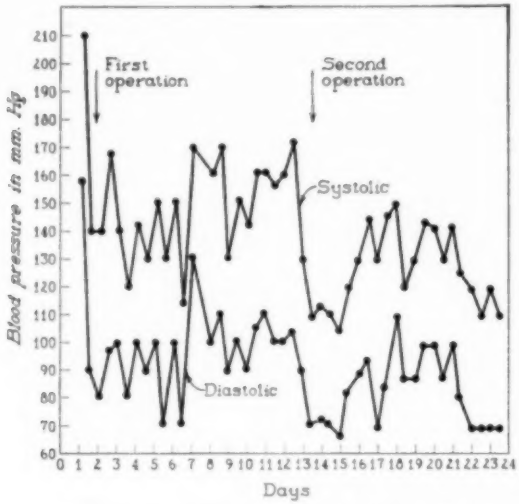

FIG. 3. Blood pressures after extensive right and left supradiaphragmatic and infradiaphragmatic sympathectomy.

In summary, from the findings during the period of observation it seemed an undoubted fact that the clinical diagnosis should be chronic glomerulonephritis of long standing which had probably been present since the patient's childhood. In recent years, however, he had severe hypertension without evidence of progressive renal disease or impairment of renal function. It was thought that, because of the very slight, if any, clinically apparent renal involvement and the acute progressive vasospastic hypertension which was present, it would be justifiable, if the patient understood the possibilities of improvement, to carry out extensive thoracolumbar sympathectomy.

On June 24, 1946, and July 6, 1946, Dr. J. Grafton Love, whose interest and coöperation greatly facilitated the making of this study, carried out extensive supradiaphragmatic and infradiaphragmatic sympathectomy on the right and left sides.

respectively, and removal of specimens from the kidneys and oblique muscle of the abdominal wall for diagnosis. The record of the blood pressures after each of these procedures is shown in figure 3.

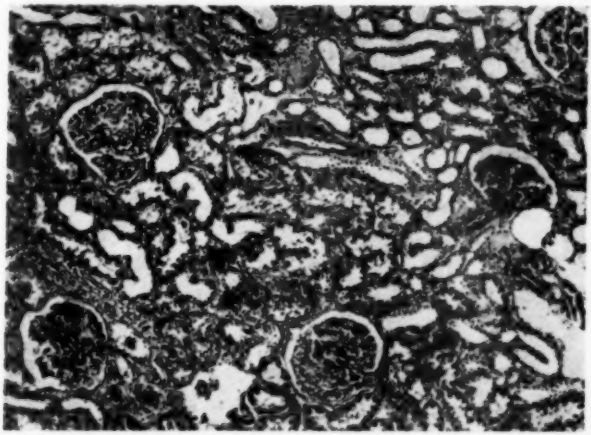

FIG. 4. Normal glomeruli of left kidney. (Hematoxylin and eosin; × 60.)

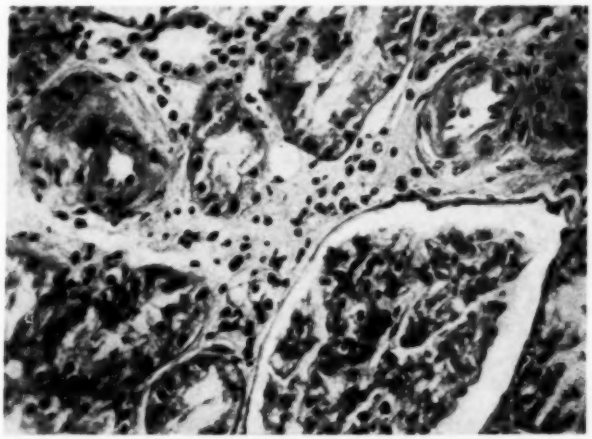

FIG. 5. Left kidney. Slight thickening of capillary basement membranes. Intimal proliferation and hyalinization of arterioles. (Hematoxylin and eosin; × 400.)

The patient's convalescence was uneventful and he was dismissed from the hospital on July 17, 1946. Studies of the blood pressure for a controlled period after that date revealed a systolic pressure of between 80 and 130 mm. and a diastolic pressure of between 52 and 90 mm. The lower levels were noted when the patient was standing. Severe orthostatic tachycardia was present. The cold pressor test

administered with the patient in the recumbent position showed an elevation of only 12 mm. in the systolic pressure and 8 mm. in the diastolic. When he was standing a rise of 12 mm. in the systolic and 16 mm. in the diastolic pressure was noted.

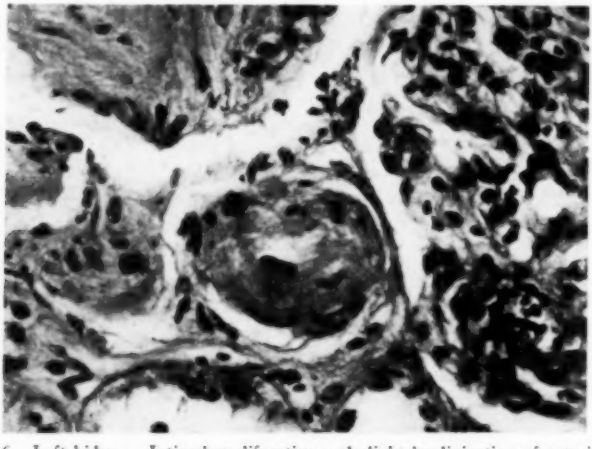

FIG. 6. Left kidney. Intimal proliferation and slight hyalinization of arteriole. (Hematoxylin and eosin; × 400.)

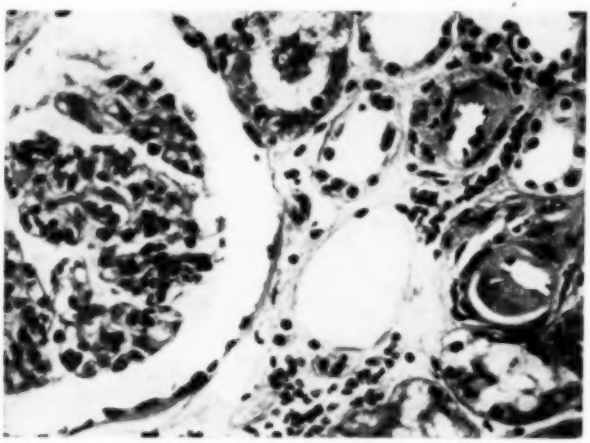

FIG. 7. Right kidney. Intimal hyalinization of arteriole. (Hematoxylin and eosin; × 300.)

Reëxamination of the ocular fundi on July 17, 1946, showed general narrowing, grade 1, of the retinal arterioles and rather minimal chronic sclerosis, grade 1. No localized spastic constrictions were seen. One residual cotton-wool patch was found in each retina and evidence of a previous punctate hemorrhage was seen on the right. Postoperatively spastic activity was markedly decreased; renal function was normal

and the values for the chemical constituents of the blood were within normal range (table 1).

The patient returned for examination in October, 1946, three months after he was dismissed from the hospital. He stated that he felt well except for shortness of breath on standing. This shortness of breath was more pronounced when he stood quietly than when he walked. He was able to walk at a normal rate for one to two miles. He had no headaches. His blood pressure was 150 mm. systolic and 112 mm. diastolic when he was lying down and 118 mm. systolic and 105 mm. diastolic when he was standing. The corresponding pulse rates were 80 and 120 beats per minute. Renal function was normal despite the persistent albuminuria. Results of laboratory studies of the blood were normal (table 1). Funduscopic examination revealed generalized narrowing, grade 1, of the retinal arterioles with minimal sclerosis, chronic hypertensive type, grade 1. No spastic vasoconstrictions were seen. No evidence of retinopathy was found. Small temporal crescents and slight retinal thickening were noted at the upper pole of the right disk.

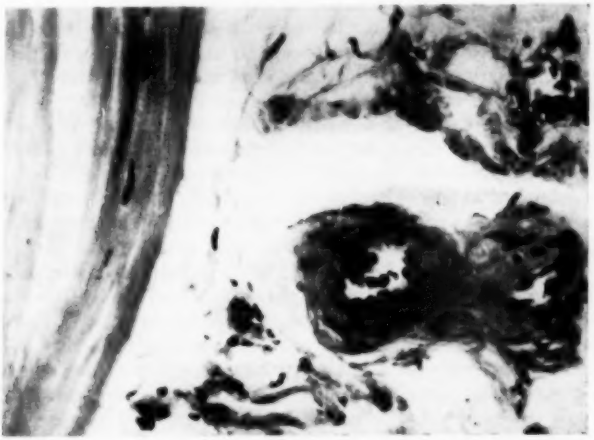

FIG. 8. Oblique muscle of abdominal wall. Slight hypertrophy of the media of small arteries. (Hematoxylin and eosin; × 350.)

Pathologic Examination of the Kidneys. At the time of operation the surgeon described both kidneys as being of normal size and shape. The color and texture were normal and scarring was not observed.

The histologic appearance of the sections of both kidneys was similar and they are described together. Most of the glomeruli appeared normal (figure 4) but occasionally a hyalinized glomerulus was seen. In a few glomeruli slight thickening of the capillary basement membranes was observed (figure 5). Evidence of intimal proliferation and hyalinization of the arterioles, grade 2 (figures 5 to 7), was found. The media of the small arteries and arterioles was somewhat hypertrophied (figures 5 and 6). The histologic picture of the kidney was that observed in cases of essential hypertension of the benign type with no evidence of glomerulonephritis.

Examination of the section of the oblique muscle of the abdominal wall revealed slight hypertrophy of the media in the walls of the small arteries, as well as some intimal proliferation (figure 8). The changes were not as marked as those in the kidney.

Comment

Despite the fact that essential hypertension and chronic glomerulonephritis are distinct diseases, sometimes the clinical picture may be so similar that distinguishing between the two may be difficult. In the presence of evidence of previous glomerulonephritis, the onset of progressive hypertensive disease with arteriolar changes and hypertensive retinitis makes the differential diagnosis even more difficult and sometimes impossible. It is important to know the phase of each disease because, as Wagener and Keith [1] have pointed out, the rapid onset of hypertension often ushers in the terminal phase of chronic glomerulonephritis. The first interesting feature of our case was that the verified history of glomerulonephritis in childhood plus persistent albuminuria for ten years afterward led to a diagnosis of a latent type of chronic glomerulonephritis. The maintenance of good renal function despite the albuminuria and severe hypertension of ten years' duration led us to suspect that the hypertension might not be entirely nephrogenic. The possibility that the severe hypertension had further affected the kidneys and that the acute angiospastic retinopathy represented the onset of terminal failure was of considerable concern to us. The findings on renal biopsy were those of primary or essential hypertension and we were probably justified in assuming that the two different disease processes were present.

The inevitable question of the pathogenesis of the hypertension which has remained unanswered through the years again arises. Johnson [2] in 1868 associated the hypertrophy of the muscular walls of the small renal arteries with the advanced stages of all the forms of chronic Bright's disease and regarded the kidney as the primary site. Gull and Sutton [3] in 1872 found the arterioles throughout the body more or less altered in cases in which the contracted kidney of chronic Bright's disease was found. They termed the alteration "hyalin-fibroid" change and observed that the changes in one case differed from those in another. They suggested that "these changes are or may be independent of renal disease and that the renal change in chronic Bright's disease with contracted kidney, when present, is but a part of a general morbid condition. These two hypotheses, suggested approximately 75 years ago, concerning the vascular changes still represent the divergent views as to the pathogenesis of hypertension: (1) that it is secondary to renal disease and (2) that the renal changes are but a part of a diffuse arteriolar disease which in turn is associated with the disease, essential hypertension.

In 1934 the hypothesis of primary renal origin was brought to the fore by Goldblatt and his associates [4] who produced experimental hypertension through renal ischemia by clamping the renal artery. Page [5] in 1939 produced severe arterial hypertension by means of perinephritis induced with cellophane. In 1937 Moritz and Oldt [6] concluded from objective examination of the arterioles in all parts of the body in 100 control cases and 100 cases of chronic hypertension that "the only significant site of arteriolar sclerosis so far as the causation of hypertension is concerned is the kidney."

In more recent years an attempt has been made to study, not only the cases of advanced hypertension and those of long duration, but cases of a less severe type of hypertension and those in which the condition was amenable to surgical treatment. Castleman and Smithwick [7] in 1943 performed renal biopsy in 100 cases of hypertension in the course of splanchnic resection. In their work the

outstanding finding was "that the morphologic evidence of renal vascular disease in more than half of the cases was inadequate to be the sole factor in producing the hypertension." This led them to think that in many cases "some other functional factor or factors exist which are primarily responsible for the hypertensive state and which precede the appearance of renal vascular disease." This view or approach to the subject of essential hypertension is the more acceptable from the pathologic standpoint. Wagener and Keith, in their discussion of diffuse arteriolar disease, agreed with those who thought that it is not of primary renal origin.

The second interesting feature of our case is that the changes in the arterioles of the muscle were not as extensive as those found in the kidneys. This finding is in keeping with the preliminary observations of Castleman and Smithwick that the peripheral vascular disease develops after the vascular changes due to renal disease. Kernohan and others [8] in 1929 pointed out that the presence of a lesion in the arterioles of muscles is indicative of diffuse vascular disease and knowledge of the degree of change may help to determine the diagnosis and prognosis in an individual case.

The third feature was the absence of any evidence of chronic glomerulonephritis in the renal specimens. Bell [9] presented six cases of chronic glomerulonephritis in which death was caused by another disease before marked renal insufficiency had developed. He stated, "These cases are of particular interest since little is known of the structure of the kidneys in the interval between the acute attack and the development of renal insufficiency." In the cases he presented some evidence of renal injury was present in all but renal function was not seriously impaired. He described the microscopic findings in one case and stated that those in the others were similar. His description follows: "About 10 per cent of the glomeruli are hyaline, and there is atrophy of their associated tubules. Practically all of the other glomeruli present a similar appearance. They are slightly enlarged and their lobulations are distinct. Under higher magnification the lobules show solid central portions with small peripherally situated capillaries. There is some increase of endothelial cells but the capillaries are not markedly constricted. The peripheral capillary basement membranes are not thickened. Glomerular filtration is evidently fairly good since there is no atrophy of the tubules associated with these glomeruli." These findings are essentially the same as those of writers on the subject of latent glomerulonephritis. The changes observed by Bell were not found in our case.

In 1925 Dawson [10] described a case of hypertension in which he had observed the patient, a girl, 22 years old, for three years. At times a trace of albumin and a few hyaline casts had been found in the urine. The patient had had a severe attack of scarlet fever in childhood. Her primary complaint was of a migraine type headache which she began to have at the age of eleven. A suggestion was made that she had slowly progressive interstitial nephritis. At operation the kidneys were decapsulated and portions of the kidneys were secured for examination. Examination of the sections showed the following: "(1) the most marked feature was hypertrophy of the tunica media of the larger arteries; (2) slight changes including some fatty degeneration of the intima of the smaller arteries; (3) patches of partial atrophy of tubules due to infiltration by small round cells

(early fibrous changes). Changes characteristic of interstitial nephritis were absent." Report of examination of these sections was made by Professor Turnbull of the London Hospital.

The great similarity between this case and the one herein reported lies in the lack of those findings in the kidney which are usually associated with chronic glomerulonephritis. To date, the kidney in the asymptomatic latent phase of chronic glomerulonephritis has not been sufficiently described. One is led to speculate that the kidney in this phase in some instances may be essentially normal in structure by present standards, yet so far as function is concerned persistent albuminuria may be present.

Summary

A case of hypertension in a white man, 29 years old, is reported. The patient had had glomerulonephritis at nine years of age which clinically had progressed to latent chronic glomerulonephritis. At the age of 19 hypertension developed. Renal function remained good throughout the course of both diseases. Bilateral sympathectomy was performed and the result was satisfactory. Biopsy of the kidney and muscle confirmed the fact that diffuse arteriolar disease was present, but no evidence of chronic glomerulonephritis was observed.

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PSYCHOSOMATIC ASPECTS OF HEART DISEASE: ANXIETY HYSTERIA IN A PATIENT WITH PATENT DUCTUS ARTERIOSUS *

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Not long ago Oille [1] said, "Almost 60 per cent of the patients who consult a cardiac specialist are suffering either from an exaggerated or wholly unnecessary anxiety about their hearts, arising from suggestion and not based on reason." Nellis [2] stated that no layman he had ever questioned had noticed a relationship between emotional stress and heart action; even medical students failed to appreciate it. Yet this relationship is so familiar to physicians that they forget its clinical implications. These statements immediately make it clear that a doctor often has to look beyond the cardiovascular system into the psyche in order to treat and understand the person who presents himself with a cardiac complaint.

It has long been accepted that the heart is the traditional seat of the emotions and thus acts as the focal point of anxiety. Anxiety neurosis is probably the most frequent disorder of civilized life.[3] It is also well known that anxiety produces such disturbances of cardiac function as palpitation, arrhythmia, tachycardia, and elevation of the blood pressure. With the onset of cardiac symptoms, attention is directed to the heart. This sets the basis for doubting the integrity of the heart that leads to a psychic reaction which seems to be more violent and profound than is the case with any of the other internal organs.[4] This is understandable, because the average layman still associates heart disease with the idea of sudden and unforeseen death. Thus the importance of the heart in the "mind's eye" is incalculable.

Weiss [3] has pointed out that the majority of patients having symptoms referred to the region of the heart show no evidence of organic heart disease. Even though organic disease be present, it may play no part in the illness. Neuhof [5] points out that patients with heart disease may get along fairly comfortably until some psychic disturbance initiates symptoms from which it may take a long time to recover. All too often we as physicians are directly or indirectly responsible for crippling symptoms on an emotional basis, even though the patient may have organic heart disease which is causing few or no symptoms. Any feelings of uncertainty about the function of the heart, arising in the patient's mind or transmitted from the doctor, may start the chain of symptoms. The statement of the physician that "you have a slight murmur" or the "heart action is irregular" or the "muscles are weak" or that "you have an athlete's heart" may furnish fuel for the fire.

Frequently the past history reveals the patient to be an emotionally sensitized individual. Conner [6] gives the following four groups of causes that may serve as a precipitating factor in the development of a cardiac neurosis:

1. The statement of some physician or life insurance examiner that the heart shows some abnormality,

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2. The occurrence of some dramatic case of heart disease (such as sudden death among relatives or friends of the patient)
3. The appearance of symptoms calling attention to the heart, and
4. Some profound and protracted emotional disturbance, such as deep grief or prolonged anxiety.

The pernicious practice of attributing symptoms to low blood pressure may kindle the first awareness of the circulation. Individuals may be particularly susceptible after an illness, when there has been a loss of muscle and vasomotor tone with weakness, postural drop in blood pressure, dizziness, and orthostatic tachycardia. Extrasystoles are more prone to occur and are more noticeable to the patient. Bed rest lends itself to introspection, and bodily functions normally unnoticed may reach conscious level.

Since cardiac symptoms may occur in neuroses of all types and even in psychoses, they are only the presenting symptoms of a more fundamental disorder—the individual's inability to handle his personal and environmental problems. The physician limiting his attention to the cardiac symptoms permits the major personality disorder to escape unnoticed and helps to fix the anxiety at a somatic level.[7]

A neurosis presents an attempt on the part of the patient to adjust to a situation that in reality is too much for him to cope with. It accomplishes something for him unconsciously that he is not consciously able to do. It is a substitution, and within this substitution lies the genesis of the patient's symptoms. In this way, as Dunbar[8] points out, ideas and experiences originally accompanied by anxiety but long since forgotten (repressed) can be the cause of disturbances in the cardiovascular system.

Just as neuroses are found in persons with normal hearts, so can they occur in individuals with organic disease. The finding of an organic lesion may blind the physician to the true cause of disability, an underlying emotional disturbance. The association of organic disease and emotional disturbances is not uncommon. Patients with congenital heart disease with murmurs or abnormalities since birth are particularly susceptible, since usually they have been overprotected and fenced in with imposed restrictions and constant reminders of their limitations. Patients with rheumatic heart disease are similarly affected, the long periods of enforced bed rest lowering the threshold of heart consciousness and giving fertile grounds for neurosis. Patients with essential hypertension are notably difficult to evaluate, psychic factors being predominant in this condition. They have been taught to expect headaches, dizziness, etc. As one patient recently said, "I know I am supposed to have these, but I do not."

Adler[9] states that in connection with psychological questions he had always noted that one of the most important reasons for lack of courage in handling problems in life is the existence of an organic burden in childhood. He points out that delicate children differ very much from the healthy in their views of the world, because they suffer from organic deficiencies and defects. Thus, feelings of personal inferiority are greatly intensified in those burdened with physical defects. To be sure, an inferior organ may even become the site of a neurosis, as is demonstrated in the case presented here.

When organic disease is present in an emotionally unstable person, one can expect to find evidence of the neurotic element in the appearance of symptoms

which cannot reasonably be ascribed to the organic disease present. Conner [10] further states that the symptoms are subjective in nature and lie outside the legitimate manifestations of the existing organic disease. When the structure of the disease is severe, the neurotic symptoms, if present, are apt to be relatively unimportant. It is in the milder forms of heart disease, with few or no real organic symptoms, that emotional reactions tend to occupy the foreground and demand serious consideration. This differentiation requires the utmost in skill, judgment, and experience on the part of a physician; how he handles this will largely determine the success or failure in the treatment of the patient. It is important to understand, as Weiss [11] explains, that the neurotic patient who has organic heart disease may add a real burden to the work of his heart, either through constant tension of psychic origin or, more especially, by means of acute episodes of emotional origin. It may hasten a cardiac breakdown which might be indefinitely postponed if there were no psychic stress. Thus, psychic factors may be more important than the physical factors producing incapacitation.

Pain is probably the most frequent subjective sensation accompanying emotional disturbances of the heart.[12] The origin of this kind of pain is usually anxiety. Evidence suggests that it may be due to faulty respiration with limited movement of the diaphragm and increased intercostal movement with accentuation by trauma resulting from impingement of the contracting heart against the intercostal muscles.[15, 16] Lipkin [13] states that the pain usually is located in the outer precordium, especially in the region of the apex, probably because most people believe the heart is located somewhere in the outer part of the left chest. Parkinson [17] has said, "No patient should ever be permitted to speak of left mammary pain as 'pain in the heart,' for it is this symptom more than any other which suggests to him the false and dangerous idea of heart disease." The pain usually is described as "sticking," "burning," "like a stitch," or as a "stabbing." In contrast to the short anginal attacks, it may last hours or even days; and it is not steady, but intermittent. It is often made up of darts and twinges. The intensity changes from moment to moment, and it is not sharply related to exertion but is more often experienced after a period of exertion rather than during exertion. It is not immediately relieved by rest or nitrites.

Dyspnea is also a very common symptom; however, if one asks the patient carefully to describe his "shortness of breath," he learns that the patient has a sense of pressure or weight on the chest. The patient states that he cannot take a deep breath, and the air that he does get in is not enough. This may be accompanied by a sighing type of respiration and even lead to the production of the so-called hyperventilation syndrome. It is here that the hyperventilation test as described by Gliebe and Auerbach [14] can be most useful, as it may even completely reproduce the patient's symptoms. The patient may complain of palpitation or "heart consciousness," which usually is manifested by tachycardia, arrhythmia, or both.

Objectively, the presence of a murmur leads to more false diagnoses of cardiac disease than any other single finding. Functional murmurs can be heard in a large number of healthy patients. This type of murmur is usually systolic in time and not associated with enlargement of the heart or great vessels. It is commonly localized, and rarely, if at all, is there any area of transmission. Usually it is located in the pulmonary or mitral areas, is blowing in nature, and varies with change of position and breathing.

If, however, there is any doubt as to the significance of a murmur, it is better not to let the patient be aware of this fact until enough evidence is found to establish the organic status of the heart. A cardiac neurosis often has its nucleus in the indiscreet remark of an examining physician who detects for the first time a systolic murmur at the pulmonic area or apex, which is unaccompanied by other evidence of organic disease.

It is essential properly to weigh the amount of disability due to physical and the amount due to emotional causes. Not infrequently when the differentiation is difficult, the physician may ascribe the disability to organic disease because of the fear of missing the diagnosis or overlooking some condition. It would seem far better to miss the diagnosis in an occasional obscure case than to condemn those with symptoms or findings suggestive of organic heart disease to the fears, uncertainty, and mixed emotions inherent in the cardiac.

Treatment should begin with the very first visit. The physician has to be fully aware not only of what he says but also of his attitude in regard to the total situation. In order to do this effectively, a careful complete history and a thorough, authoritative physical examination is necessary. Laboratory procedures should be done only when indicated. Then a frank discussion should be held with the patient. Great care should be taken not to over-estimate the organic disease when present. If an electrocardiogram or roentgen-ray examination is necessary, the necessity should be explained. If no organic lesion is found, the physician should speak frankly about this and explain how emotional stress can produce physiological responses in the cardiovascular system. If one is in doubt as to the diagnosis and consultation is thought to be needed, this, too, should be explained. The whole object is to reach a positive diagnosis as soon as possible, and then treat accordingly. If the problem is a difficult emotional one, psychiatric help should be sought. If primarily organic, it should be handled accordingly. In some cases, both the organic and psychic problems will demand expert care. Treating the patient as a whole is the only way of handling the situation successfully, and it may prevent the patient from falling into that not too uncommon group of heart diseases produced by the physician.

Case Report

Mrs. C., a 39 year old married white female, was admitted to the hospital on January 30, 1947 with a history of being confined to bed for the previous three years because of heart trouble. At the age of fifteen she was said to have had a "heart attack" and was taken to a local hospital, where, during the course of examination, a murmur was found. She was told that this was the cause of her trouble, and that she would have to live a restricted, cautious life. Since then she has had recurrent "heart attacks" characterized by extreme shortness of breath, a sense of suffocation and weight on her chest, palpitation, numbness and tingling in her arms and legs. With her first attack she remained in bed one year, and after an interval of one year she went to bed for seven years. She recovered enough to be up and around for about 12 years. During the previous three years, she had been at complete bed rest, the slightest bit of exertion producing attacks. For two years she had been on a diet of goat's milk and soft food, because of epigastric discomfort occurring one to two hours after eating. Her mother died of a heart attack, and her sister is said to have heart trouble.

Physical examination revealed a thin, anemic, tense, malnourished woman. The blood pressure was 138 mm. Hg systolic and 88 mm. diastolic in the right arm, and

148 mm. Hg systolic and 92 mm. diastolic in the left arm. The temperature was 103° F., pulse 92, and respirations 22. The significant physical findings were as follows: There was a severe pyorrhea of the gums. The teeth were in poor repair, and there was moderate fetor oris. The lungs were clear. The heart size was normal. There was a typical machinery murmur of a patent ductus arteriosus heard in the second left intercostal space; no thrill was palpated. The rhythm was regular, and the rate was 92. Her weight was 96 pounds. The remainder of the physical examination was normal.

Fluoroscopic examination showed the heart to be of normal size. The pulmonary artery segment was normal with no increased pulsations. The electrocardiogram revealed an unimportant degree of left axis deviation. The urine examination was normal. The red cell count was 4.67 million, with 88 per cent hemoglobin. The white cell count was 6,000 with an essentially normal differential. The Kahn was negative. The sedimentation rate fell 7 mm. in one hour.

Hyperventilation reproduced the so-called heart attacks. The symptoms rapidly subsided upon rebreathing carbon dioxide. A diagnosis of severe chronic anxiety hysteria, with hyperventilation attacks was made. Although the patient had organic heart disease due to a patent ductus arteriosus, there was no evidence of impaired cardiac reserve. The patent ductus was incidental to a severe psychoneurosis.

Psychiatric study revealed that the patient was an emotionally unstable person long before her first "heart attack" took place. Her home situation was an unhappy one. She described her father as being "unaffectionate"; "strict"; a "puritan-primitive" kind of man. Her mother was not very demonstrative of her affections. Her parents were not happy themselves.

When only fourteen and a half, she married a man of thirty-nine. When asked why she did this, she said that he was "nice to me"; he was "affectionate"; he was "like a father." A very short time after her marriage, however, she was faced with the reality that he did not love her. This marriage ended in a divorce.

About three months after her marriage, she developed a rash. In spite of negative serological tests on the blood and spinal fluid, she was reminded by her doctor that she still might have syphilis. Actually, the rash turned out to be due to bromides.

One month before her first spell, her father died, and this upset her a great deal. About the same time her sister, who was supposed to have heart disease, had an abortion and "nearly died with it." Just prior to her first "heart attack," she thought, "What a mess the whole situation is." As soon as the diagnosis of a murmur and heart disease was made, a somatic crutch was given to her upon which she focused all her anxiety, and everything soon became "my heart condition."

After a year in bed she began to recover slowly. She realized that she didn't love her husband, but he plagued her constantly and produced many embarrassing situations. The only time she felt safe and secure from him was when she was sick in bed. As his threats became more persistent, she spent more and more time in bed, finally remaining there for seven years!

It is interesting to note that around her seventh year of bed rest, her husband made it clear that he no longer wanted her and would like to have a divorce. With this turn of events, her fears began to disappear, and improvement occurred.

Shortly after this, she met her present husband. As this friendship developed and the threat of her first husband passed, she finally got out of bed. Her friendship with Mr. C. culminated in marriage in February of 1941, shortly after her divorce from her first husband became final. She did not marry Mr. C. for love, but for "practical reasons." He was "nice," "seemed to like me," and "wanted to look after me."

Then a new turn of events began. She had been told by her doctor that she

should never become pregnant, because she would be unable to carry the pregnancy, and she might even die with it.

In December of 1942 she became pregnant. This ended in a therapeutic abortion. One year later in December, she again became pregnant and had a second therapeutic abortion. She never quite recovered from this. Her fear of pregnancy mounted, and this was solved by returning to complete bed rest.

In July 1944, her mother died of a "heart attack." With her mother's death, she gave up all hope. The attacks became more frequent than ever before. She dreamed about her mother constantly and developed a tremendous guilt complex. She felt that she was responsible for her death and should have done a lot of things for her that she had not done while she was alive.

Before coming to the hospital, she asked her physician what possibly could be done for her. She was told frankly that nothing could be done. It was with an attitude of hopelessness that the patient came to the hospital.

Treatment consisted of daily therapeutic interviews with and without hypnosis, occupational and physical therapy, and a high caloric diet supplemented by iron and vitamins. Using these technics, the patient was able to get out of bed after her first interview under hypnosis but had to relearn to walk. With the liberation of her repressed hostilities and a change in outlook of life, she made rapid progress. She gained in weight from 96 pounds to 108 pounds. Her heart rate and temperature became normal. Whereas five months prior to her admission to the hospital she had been taking large amounts of sedatives during the day and night, she was discharged with no sedation. Whereas she entered the hospital in an ambulance, being unable to walk, she left fully ambulatory. Thus, during a five week period, she learned that her trouble was not in her heart literally speaking, but that her major problem was a chronic emotional one.

The patient was seen again a month after her discharge and was happier than she had been in years.

In summary, we find that the patient was born with an inferior organ, her heart. She was emotionally unstable from childhood, having experienced much emotional trauma. At 15 she had her first overt anxiety "heart attack" which drew attention to this organ. Her anxieties were confirmed by doctors when she was told that she had a murmur and would have to spend the rest of her life taking it easy. Then there were the many years of bed rest—11 years in all—with the repeated confirmation by doctors that her trouble lay in her heart. This is an example of the inferior organ being the center of the neurosis. On studying the patient as an individual, she was found to have organic heart disease, but in addition she had been suffering from a severe chronic anxiety hysteria neurosis since age 15. Only by treating her as an individual was she able to express her repressed hostilities, develop a new outlook on life, and then return to a useful existence.

Summary

A case of long standing anxiety hysteria occurring in a 39 year old patient with patent ductus arteriosus is reported. The emotional influences underlying the illness are studied, and comments are made on the functional aspects of organic heart disease.

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STREPTOMYCIN TREATMENT OF BACTERIAL ENDOCARDITIS DUE TO *STREPTOCOCCUS VIRIDANS;* REPORT OF TWO CASES*

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The precise place of streptomycin in the treatment of bacterial endocarditis has yet to be definitely established. It has been proposed [1] as the drug of choice in cases caused by gram-negative bacilli susceptible, at least in vitro, to streptomycin. It must also be considered, however, in the small fraction of cases due to nonhemolytic streptococci in which the organism is initially resistant to penicillin, as well as the still smaller fraction, where penicillin resistance develops during therapy.

Relatively few reports [1, 2, 3, 4] have appeared concerning the use of streptomycin in bacterial endocarditis, and the percentage of these cases due to penicillin resistant *Streptococcus viridans* has been low. The following two cases are considered worthy of addition to the literature for two reasons: they illustrate apparent cure of such infections without significant toxic effects; and they demonstrate the balance necessary between clinical judgment and the utilization of in vitro tests of streptomycin sensitivity in determining the course of therapy.

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Case Reports

Case 1. A 20 year old white merchant seaman was admitted to the U. S. Marine Hospital, Staten Island, N. Y., on May 11, 1946, complaining of pain in his joints. Except for a questionable episode of rheumatic fever at the age of nine, the patient had been well until two years prior to admission, when he began to note intermittently, migratory polyarthritis and fever. In January 1945, while under observation in another hospital following a blow to his head, he had an apparently typical attack of rheumatic fever, and was told by his physician that he had a heart murmur. After three months' hospitalization, he remained asymptomatic until May 9, 1946, when polyarthritis of increasing severity, and marked fatigue were noted. Chills and fever were first observed by the patient on the morning of admission.

The only positive findings disclosed on initial physical examination were a blood pressure of 155 systolic, 0 diastolic, temperature 101° F., pulsating neck veins, and harsh systolic and diastolic murmurs over the aortic and mitral regions of the heart.

The red cell count was 5,100,000, with a hemoglobin of 16 grams. The white cell count was 7,200 with a differential count within normal limits. Complete examination of the urine was negative. Mazzini and Kahn tests were negative. Roentgenogram of the chest was normal. The electrocardiogram showed a PR interval of 0.20, with elevated $ST_{2 \text{ and } 3}$ segments. Sedimentation rate (Cutler method) was 17 mm. in one hour.

Despite intensive salicylate therapy, joint pains and weakness persisted, while the temperature daily spiked to 101° to 102° F. On June 5, a subungual splinter hemorrhage on the index finger of the right hand, a typical Osler node on the fifth finger of the left hand, and several petechiae on the left great toe were observed. Five days later, conjunctival petechiae appeared, and the spleen became palpable. The white cell count rose to 16,700 with 80 per cent neutrophiles, 14 per cent lymphocytes and 5 per cent mononuclears. Sedimentation rate was found to be 28 mm. in one hour.

The blood was cultured on June 5, 6 and 10, and the presence of typical alpha hemolytic streptococci (*Streptococcus viridans*) was disclosed in each specimen. Initially the cultures showed 30 colonies per c.c. of blood. The organism appeared to be sensitive to penicillin in a range from 0.07 to 0.15 unit per c.c., and treatment with penicillin was begun, giving 160,000 units intramuscularly every two hours. On June 11, however, a report was received that some of the organisms first cultured were continuing to grow in penicillin concentrations of 2.0 units per c.c. It was eventually determined that these organisms were not completely inhibited even in concentrations of 10.0 units per c.c. Penicillin was thus discontinued after 10 doses had been given, and streptomycin was begun, 0.25 gram being administered intramuscularly every three hours.

On June 12, cultures showed two colonies of *Streptococcus viridans* per 5 c. c. of blood. These organisms were markedly inhibited by four units of streptomycin per c.c., and completely inhibited in concentrations of 8 units per c.c. Serum streptomycin levels on June 14 were found to be 30 units per c.c. after one hour, and 20 units per c.c. two hours and 45 minutes after injection of 0.25 gram. On June 15, after 10 grams of streptomycin had been given, the dosage was increased to 0.3 gram every three hours. Blood culture was negative on June 17, and repeated cultures continued so throughout the remainder of hospitalization. Serum streptomycin levels on June 20 were 40 units per c.c. after one hour, and 20 units per c.c. three hours after injection of 0.3 gram.

Marked clinical improvement was noted 24 hours after beginning streptomycin therapy. The patient became afebrile, and rapidly regained a sense of well being, which he maintained. Subsequently, repeated white cell counts and sedimentation rates were within normal limits. Except for transient urticaria, first noted on June 21, and relieved by the use of benadryl, no toxic effects of streptomycin were observed.

Streptomycin was discontinued on July 6, after a total dosage of 58 grams had been given. Twelve consecutive negative blood cultures were obtained, and the patient was discharged on August 20, 1946, apparently cured.

Repeated blood cultures in January, 1947 and again in July, 1947 were negative and the patient remained clinically well and active.

Case 2. A 29 year old white male factory worker and World War II veteran was admitted to the U. S. Marine Hospital, Staten Island, N. Y. on December 14, 1946, complaining of pain in his left upper abdomen. The patient had had rheumatic fever at the age of 13, but was otherwise well until two months prior to admission, when he began to note weakness, anorexia and weight loss, following a brief febrile illness described by him as influenza. One month later intermittent short attacks of left upper quadrant abdominal pain began, accentuated by deep breathing. During the week preceding admission, this pain became relatively constant. In this interval too, the patient noted chills and fever, and transitory red spots on the palms of both hands. Total weight loss reached 20 pounds, and the patient was told by his private physician that his hemoglobin was 58 per cent.

Physical examination on admission revealed an acutely ill, pale, anxious young white male with a blood pressure of 122 systolic and 62 diastolic, temperature 100° F., and pulse 110. The lungs were clear to percussion and auscultation. The heart was not enlarged; a soft blowing systolic murmur was heard over the apical region. The spleen was not definitely palpated, but marked tenderness was evident on pressure over the left upper quadrant of the abdomen. A small tender ecchymotic area was present in the left palm. No other significant findings were disclosed.

The red cell count was 3,700,000 with a hemoglobin of 12 grams. Differential white cell count was within normal limits. Initial urinalysis was negative, but the following day showed 12 to 15 red blood cells on microscopic examination. Mazzini and Kahn tests were negative. Combined fluoroscopy and radiography of the chest showed some prominence of the left ventricular segment of the heart, with expansile pulsations of the aorta; the lung fields were clear.

On December 15 a blood culture showed the presence of typical *Streptococci viridans*. Pending the results of sensitivity tests of this organism, penicillin therapy was begun on December 16, giving 50,000 units intramuscularly every two hours. Sulfadiazine and sulfathiazole were also simultaneously begun, but were discontinued the following day, after 10 grams of each had been given. At that time, conjunctival petechiae, a small left retinal hemorrhage, and a loud systolic murmur at the base of the heart were first observed. The patient's temperature fluctuated between 99 and 101° F. until December 19, when it fell to normal. Meanwhile, culture of a blood specimen obtained on December 16 was also reported to show *Streptococcus viridans*. On December 20 a report was received that these organisms were resistant to at least five units of penicillin per c.c., but were completely inhibited by 16 units of streptomycin per c.c. Penicillin was thus discontinued after 2,400,000 units had been given, and streptomycin was begun, 0.5 gram being administered intramuscularly every three hours.

Blood culture on December 24 was negative, and frequently repeated cultures continued so throughout the remainder of hospitalization. Serum streptomycin concentrations from two and one-half to five times that required to inhibit the organism in vitro were obtained during therapy, reaching levels on December 26 and January 12 of 40 and 80 units per c.c., respectively, two and three-quarter hours after injection of 0.5 gram of streptomycin.

On January 2, 1947 urinalysis was negative, white cell count was 15,000 and the sedimentation rate was 28 mm. in one hour. By February 19, however, the white cell count and sedimentation rate returned to normal limits. The patient rapidly regained his strength and appetite, along with complete subsidence of abdominal pain

and tenderness, but he began to complain of dizziness on motion two days after beginning streptomycin therapy. Streptomycin was discontinued on January 20, after a total of 123.5 grams had been given. No further signs of toxicity were observed, and the patient became ambulatory without difficulty. A positive Romberg sign was elicited on February 6, and this persisted until the patient was discharged on March 6, 1947, but he remained otherwise clinically well.

Discussion

There is considerable evidence [5, 6, 7] that at present penicillin is the drug of choice in the treatment of bacterial endocarditis due to *Streptococcus viridans*. In two of the largest series [5, 6] of cases of subacute bacterial endocarditis reported, this organism was found to be sensitive to penicillin in a range from 0.008 to 0.28 unit per c.c. There are, however, a small group of cases of extremely high in vitro resistance to penicillin. In that portion of these cases in which the organism is susceptible in vitro to streptomycin, it seems reasonable to attempt prolonged and intensive streptomycin therapy.

In treating cases of this disease with penicillin, it has been recommended [7] that enough penicillin be employed to obtain a blood level at least five to 10 times the minimal amount effective in vitro. Dawson and Hunter [8] found that the serum level of penicillin could be predicted with reasonable accuracy from the daily dose of penicillin. Thus 200,000 units daily, administered by constant intramuscular drip, produced an average serum level of 0.07 unit per c.c.; 1,000,000 units produced a level of 0.56 unit per c.c.; and 10,000,000 units produced a level of 6.6 units per c.c. In both cases reported here, the organisms were unusually resistant to penicillin, and it was felt impossible to obtain adequate blood levels of this drug. Recently, however, Boger et al.[8] found that with the aid of caronamide it was possible to give 4,000,000 units of penicillin daily by intermittent intramuscular injection, and yet obtain plasma concentrations of 30 to 60 units of penicillin per c.c.

In the cases of this report, large doses of streptomycin were employed from the beginning of treatment with this antibiotic. This was felt to be particularly important, because of the marked tendency of organisms to develop resistance to streptomycin. Transitory urticaria, and possibly permanent but mild vestibular dysfunction were noted as toxic effects of this therapy, while no other serious toxic manifestations [9] of streptomycin administration were observed. Audiometric and vestibular function tests were unfortunately not done, but it is recommended that they be carried out in any similar future cases.

Although careful bacteriologic control and adequate in vitro tests of streptomycin sensitivity are extremely important, the outcome of therapy cannot always be predicted from the results of these tests. In the first case reported here, 8 units of streptomycin per c.c. were required to completely inhibit the causative organism in vitro, and in the second case, 16 units per c.c. were necessary. These high levels were initially discouraging, but it was felt that a trial of streptomycin therapy was still justified, in view of the poor prognosis of the patients after the failure of penicillin. Actually, the concentration of streptomycin maintained in the blood ranged from two and one-half to five times that required to inhibit in organism in vitro, and clinical cure resulted.

In Hunter's [7] recent report on the use of streptomycin in bacterial endo-

carditis, which included six of his own cases and 12 more supplied to him by Dr. Chester Keefer, only four cases were due to *Streptococcus viridans*. Streptomycin was given for a duration of 14 to 34 days, with a total dosage ranging from 17 to 103 gm. Questionable cure resulted in two cases, while failure occurred in the others.

Of the cases reported earlier by Priest and McGee,[2] only one was due to a typical *Streptococcus viridans;* 2.5 grams of streptomycin were given over a five day period, before the patient died.

Boger et al.[8] reported a case of subacute bacterial endocarditis due to *Streptococcus viridans,* resistant to 69 grams of streptomycin over a 23 days period, but eventually responding to combined intramuscular penicillin and oral caronamide.

A search of the available literature has failed to reveal any other cases of bacterial endocarditis due to typical *Streptococcus viridans,* treated with streptomycin.

Summary

Streptomycin was successfully used in the treatment of two cases of bacterial endocarditis caused by typical *Streptococcus viridans.*

The causative organism was isolated in each case and determined to be relatively insensitive to penicillin in vitro, but sensitive to concentrations of streptomycin that could be, and actually were, clinically attained.

Addendum

Follow-up study of the patient V. M. (Case 2) 19 months after discharge from the hospital revealed that he had remained clinically well. Residual vestibular dysfunction had subsided. Urinalysis, complete blood count and electrocardiogram were within normal limits. Roentgenogram of the chest showed no significant change in comparison with previous films. Three blood cultures were negative.

The author wishes to thank Dr. R. H. Smith, Chief of the Medical Service, U. S. Marine Hospital, Staten Island, New York, for his suggestions and helpful advice.

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TOXICITY OF THIOCYANATES USED IN TREATMENT OF HYPERTENSION *

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THE purpose of this article is to describe the toxic effects of thiocyanate as used in the treatment of hypertension, and to report a fatal case of thiocyanate poisoning.

HISTORY AND GENERAL USAGE

The popularity of thiocyanate (SCN) treatment for hypertension has fluctuated over a period of years. The drug was first studied from a pharmacological standpoint in 1857 by Claude Bernard, but it was not until 1903 that Pauli made use of its hypotensive properties in clinical medicine. In 1925, Westphal commented on its toxic effects. In 1929, the Council on Pharmacy and Chemistry of the American Medical Association refused to accept the Elixir and Tablets of Potassium Thiocyanate for inclusion in the New and Non-official Remedies, because of their toxic qualities.[1] Since that time, however, there has been a resurgence of its use, and several fatal and non-fatal cases of poisoning have been reported. Recently, two new proprietaries which contain thiocyanate, "Thiocara" and "Hypersed," have appeared on the market.

In hypertension, thiocyanate reduces the systolic and diastolic blood pressures by 60 and 40 mm. respectively, is effective against headache, and may produce a feeling of general well-being.[22, 23, 24] The drug is given by mouth in 0.2 gram doses sufficient to maintain a blood level of from 5 to 14 mg. per cent. Weekly blood assays are made, and the patient closely observed for signs of toxicity, particularly a maculopapular eruption and toxic psychosis.

CLINICAL STUDIES

Goldring and Chasis [3] reported on the toxic effects of thiocyanate in a carefully studied series of 69 cases of essential hypertension, and five cases of glomerulonephritis. Thirteen of the 74 cases showed toxic symptoms. Six of these patients developed a toxic psychosis, and of these, two died. There were three cases of motor aphasia apparently due to the drug.

These authors found that the toxic symptoms, in the order of their appearance, are: muscular fatigue, followed by nausea and vomiting; disorientation, mental confusion, motor aphasia, hallucinations of sight and hearing; in fatal cases progression to delirium, convulsive twitchings and death. They quote the work of Nichols [4] who observed a similar march of objective symptoms in guinea pigs. Nichols postulated a strychnine-like action of thiocyanate because of the muscular irritability, twitchings and convulsions. Russell and Stahl,[5] in discussing their fatal cases who had jerking motions of the extremities, stress the convulsive action of thiocyanate.

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Psychosis is extremely common in intoxication with thiocyanate,[27] almost all fatal cases having been preceded by confusion, hallucinations, delusions and psychomotor agitation. Mental symptoms are therefore very significant from a prognostic point of view. Although only three cases of toxic psychosis who recovered have been reported, [6, 27, 7] internists of wide experience state that mental abnormalities during treatment with thiocyanate are relatively frequent.[8]

Others have described the goitrogenic action of thiocyanate. This effect was first noted in rabbits that were fed a diet of cabbage, which contains cyanide in small quantities. Cyanide is partially detoxified to thiocyanate in lower animals and man.[2] Ingestion of foods of the cabbage family probably accounts for the presence of a blood level of 0.030 to 0.060 mg. per cent of thiocyanate in normal men. In human hypertensives, acute diffuse goiter with pain and myxedema have been reported [9, 10] as well as acute enlargement of an adenomatous nodule of the thyroid and chronic diffuse goiter.[11] Thiocyanate produces goiter by a mechanism similar to that of thiouracil.[28] The goiter similarly responds to administration of thyroid.[21]

Coryza-like symptoms have been noted. The skin manifestations of toxicity include pruritus, a maculopapular eruption [11] and exfoliative dermatitis.[12] A maculopapular eruption is one of the earliest and most common toxic signs.

Acute allergic phenomena from thiocyanate include edema of the glottis and larynx.[13] Friedman's patient,[14] who received 18 grams of thiocyanate in six weeks, developed a skin rash with a high eosinophilia, and died. At autopsy, a Fiedler's myocarditis was found, with nodules the size of rice grains throughout the heart, each nodule consisting of masses of inflammatory cells around areas of liquefaction necrosis, and giant cells and eosinophiles at the periphery.

Thrombophlebitis was a relatively frequent complication of long term thiocyanate therapy in the cases studied by Koffler.[15] Of 40 patients, four developed thrombophlebitis. Friedman reports this complication with even small doses of the drug.

A case of subacute glomerulonephritis who had received a total of 3.31 grams in 11 days was reported as a fatality due to thiocyanate.[16] The patient showed frank hematuria and a typical psychosis, and died in renal failure. Bloody diarrhea has also been reported.[17] A fatal case contributed by Weeks showed a subdural hematoma in the absence of signs of trauma.[18]

Kotte, who studied the effects of thiocyanate on animals and in the clinic, and noted no beneficial results, quotes Davis and Barker, who found that prolonged administration of this drug reduces the blood cholesterol, the serum proteins and the red cell count.[13]

A total of 14 deaths due to this drug have been reported previously.[14] Autopsied cases showed no specific anatomical changes which could be directly attributed to thiocyanate. In the autopsied case of Chasis and Goldring, an unusually high level of drug was demonstrated on chemical analysis of the internal organs. The lung tissue contained 17 mg. per 100 grams of tissue, kidney 15 mg. per cent, liver 14 mg. per cent, heart 9.7 mg. per cent. Analysis of the organs of an individual who had not received thiocyanate yielded 4 mg. per cent in the liver and a trace or none in the other organs.

The following case is the fifteenth fatality:

*Case 2: Fatal Thiocyanate Poisoning.** A 46 year old pharmacist was admitted to another hospital on August 10, 1945, because of dyspnea, palpitation and sweating, which had lasted for eight hours. He had been well until a year before admission, when he first complained of severe headaches in the frontal and occipital regions. On consulting a doctor, he was told that his blood pressure was "240."

On the first admission, he was severely ill, breathing rapidly, with a pulse of 124 and blood pressure of 260 mm. of mercury systolic and 130 mm. diastolic. The eye grounds showed arteriosclerotic changes, hemorrhages and papilledema. The heart was enlarged to the left, and there was a protodiastolic gallop. There were wheezes throughout both lungs and edema of the ankles. The blood non-protein nitrogen was 38 mg. per cent. An intravenous pyelogram was negative.

A diagnosis of essential hypertension was made. He was proposed for treatment by the Smithwick technic of sympathectomy.

However, six days after admission, he suddenly became unable to speak. At that time, his blood pressure was 270/120. No other signs indicative of a focal lesion in the brain were reported. The aphasia disappeared in three days.

A week later, he was "not considered to be a suitable candidate for sympathectomy, because of the cerebrovascular complications, the high diastolic pressure and a poor response to cold, posture and sedation." He was discharged, and returned to this city.

He then came under the care of another physician, who prescribed Elixir of Potassium Thiocyanate USP, digitalis, mercupurin and a salt-free diet. Dosages are not known. However, he soon became "delirious and unmanageable" and had to be transferred to Bellevue Hospital on September 25, 1945.

On admission, his state of consciousness was clouded, so that he was able to respond poorly, and then only to urgent commands. He could make sounds, but was unable to speak words. The pulse was 116, temperature 101.2° F., and blood pressure 220/120. The right hand and right leg were weaker than the left, and there was a "claw" deformity of the right hand. A rough systolic murmur, suggestive of a friction rub, was heard at the apex. The liver was enlarged. Other physical findings were similar to those of two months previously.

The urine was of low specific gravity and contained protein and casts. The blood urea nitrogen was 37.7 mg. per cent, creatinine 2.5 mg. per cent and thiocyanate 25 mg. per cent. (Normal value 0.030 to 0.060 mg. per cent.)

By the third hospital day, Cheyne-Stokes respiration was noted. There were muscular twitchings throughout the body, with positive Chvostek signs. The signs of Chaddock and Oppenheim were elicited on the right leg. The CO_2 combining power of the blood was within normal limits. Blood chemistry figures (in mg. per cent) were as follows:

TABLE I

Date	SCN	Blood Urea Nitrogen	Creatinine
Sept. 26, 1945	25	57.7	2.5
Sept. 28, 1945	21	39.6	2.8
Oct. 1, 1945	11.1	34.5	3.0
Oct. 2, 1945	Died		

Clinically, his condition grew steadily worse. He went into peripheral vascular collapse and died on the seventh hospital day. Final diagnoses were: (1) Thiocyanate poisoning; (2) essential hypertension; (3) infarction of left internal capsule.

* *Case 1: Toxic Psychosis Due to SCN* has been reported previously.[27]

A complete autopsy was done. Positive findings included a recent infarct of the cardiac apex, and passive congestion of the liver and spleen. The kidneys weighed 170 and 160 grams respectively. Their capsules stripped easily, but the renal surface showed multiple white scars. Many of the glomeruli were atrophic and hyalinized. The walls of the blood vessels were markedly thickened, with narrowing of their lumina. There was much fibrosis between the tubules. An anatomical diagnosis of arteriolar nephrosclerosis was made.

Examination of the brain * showed sclerosis of the circle of Willis. Both occipital lobes showed areas of cortical softening, and there was softening of the left caudate nucleus and several softenings in the cerebellum. Microscopically, there was fibrosis and endarteritis of the pia-arachnoid. There were areas of early softening around some of the arterioles with actual necrosis of the brain tissue in places. There were many small areas of hemorrhage in the gray matter. Fat stain showed an increase in fat in the gray matter. These findings are compatible with arteriolar sclerosis and arteriosclerosis, followed by infarction.

Laboratory Data

The minimum lethal dose of sodium thiocyanate, given in a single dose to healthy guinea pigs, is between 200 and 400 mg. per kilogram of body weight.[4] A proportionate minimum lethal dose for an average size man would be 15 to 30 grams. However, this drug is used on individuals who frequently have impairment of their renal function and therefore an impairment in their ability to excrete the drug. In patients with depressed kidney functions, one may then expect the fatal dosage to be somewhat below 15 grams, provided that the time during which the drug is administered is not taken into account. In the eight cases of fatal poisoning in which the exact dosage is known, the amount of thiocyanate ingested has been 3.31 grams, 8 grams, 9 grams, 12 grams, 15 grams, 15 grams, 18 grams, 25 grams.[16, 3, 19, 5, 2, 20, 14, 17]

Some observers utilize the blood level as a guide to toxicity. Barker (who introduced the determination of thiocyanate in the blood) and his associates felt in 1939 that "no case of severe intoxication appeared at a blood level below 20 mg. per cent." [21] From their experience with about 300 cases, they report that the optimum blood level is between 8 and 14 mg. per cent. Massie, Etheridge and O'Hare found that the optimum level was 5 to 7 mg. per cent.[22]

The blood level would be an accurate indicator of the amount of drug in the body if renal excretion were uniform and rapid. However, Goldring and Chasis found that the average daily excretion of thiocyanate in the urine varied from individual to individual by over 500 per cent; Wald, Lindberg and Barker report a variability of 400 per cent. Peters, using human subjects, and Homer Smith, using dogs, found that the renal clearance is "extremely small and variable, ranging from 0.3 per cent to 2.0 per cent of the filtration rate of thiocyanate." About 90 per cent of blood thiocyanate is available for filtration.[23]

Data on toxicity show a corresponding degree of variability. Two similar cases of hypertensive cardiovascular disease developed a toxic psychosis, one after receiving 24 grams of thiocyanate in 18 days, the other 26 grams in 60 days.[6, 7] The blood level is of secondary value in cases of drug sensitivity. Friedman's case showed a blood concentration of 3.3 mg. per cent when symp-

* The brain was examined by Dr. L. D. Stevenson, Director of Neuropathology, Bellevue Hospital.

toms were well established. Koffler's first case of thrombophlebitis had a blood level of 6.4 mg. per cent.

Most important of all, deaths have resulted from thiocyanate in cases where the blood level was within what is generally considered the safe range—3.3 mg. per cent, 4.2 mg. per cent, 7.0 mg. per cent.[14, 5, 20] A case of toxic psychosis developed when the blood level was 12 mg. per cent.[7]

The total amount of thiocyanate in the tissues at the first sign of intoxication has been studied by the method of measuring the total urinary output, and subtracting this figure from the quantity of drug administered. In four essential hypertensives so studied, there was a variability of about 600 per cent in the residual drug in the body at the time when toxic symptoms first appeared.[8]

TABLE II

Case	Total Dose at Time of Intoxication, grams	Residual SCN in Body at Time of Intoxication, grams	Daily Dose, grams	Days of Treatment	Fall in B.P. at Time of Intoxication
5	12.7	5.0	0.9	13	No
6	5.9	3.2	0.6	9	No
7	26.6	21.5	1.2	22	Yes
8	9.8	8.5	0.6	15	No

The quantity of thiocyanate in the tissues may also be estimated from the blood level by using the known ratio between plasma volume and the volume of the extracellular tissue fluid. However, in cardiac and renal disease, found so frequently in patients with hypertension, there is a disturbance of this ratio.

Laboratory data, therefore, furnish only a general estimate by which we may regulate thiocyanate dosage. Careful observation of the patient will detect the first sign of toxicity, but by the time that intoxication has appeared, a quantity of drug will have been stored in the body tissues, and the period of intoxication will be prolonged.

SUMMARY AND CONCLUSIONS

1. A fatal case of intoxication by thiocyanate used in hypertension is reported.

2. A review of the literature shows that the principal toxic reactions from thiocyanate include dermatitis, psychotic symptoms, thyroid enlargement, thrombophlebitis, convulsive twitchings, and death.

3. Because toxic symptoms are frequent, severe, and cannot be satisfactorily predicted by laboratory studies, thiocyanate is to be considered a potentially dangerous drug.

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MASSIVE PERIRENAL HEMORRHAGE IN PERIARTERITIS NODOSA *

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PERIARTERITIS nodosa has been described with increasing frequency during the past two decades. It is probable that this apparent increase reflects a wider recognition of the entity both clinically and pathologically. The great diversity of symptoms and pathologic processes characteristic of this disease results from the widespread distribution of the vascular lesions which are responsible for the secondary visceral reactions.

Although the kidney is involved more frequently than other organs,[1] massive perirenal hemorrhage is an unusual complication of periarteritis nodosa. We have been able to find nine such cases reported.[2, 3, 4, 5, 6, 7, 8, 9, 10] In two of these [2, 9] the hemorrhage was bilateral, as in the following case:

CASE REPORT

A 47 year old white male was admitted to the service of Dr. W. A. Bradshaw at the Presbyterian Hospital on April 11, 1946 complaining of severe epigastric pain of four days' duration. The onset was abrupt following a 10 day period of vague epigastric discomfort. The pain radiated posteriorly and gradually decreased in severity over a period of 10 to 14 hours. During the few days before admission the patient was frequently nauseated, and on several occasions he vomited small amounts of bile stained fluid. The pain was uninfluenced by food, alkalis, or by vomiting.

For 10 years the patient had frequently experienced attacks of "indigestion" which were relieved by alkalis. In addition, he complained of occasional cough, shortness of breath, pain in the chest unrelated to exertion, and swelling of the ankles in the morning.

The physical examination disclosed moderate epigastric tenderness, without rigidity or palpable masses. The pulse was regular at 60 per minute and the heart sounds were normal. The blood pressure was 160 mm. Hg systolic and 85 mm. diastolic. The temperature was normal, and respirations were 24 per minute.

Laboratory studies on admission revealed an acid urine with a faint trace of albumin. The specific gravity was 1.016. The red blood cell count was 3,900,000 per cu. mm.; the hemoglobin content was 11.3 gm./100 c.c. (Haden-Hausser). The white blood cells numbered 4,750 per cu. mm. The non-protein nitrogen and sugar content of the blood were within normal limits. The icterus index was 6 units. Serologic tests for syphilis were negative. The blood amylase was 4 units (Winslow). The sedimentation rate was 32 mm. in 60 minutes (Cutler). A roentgen-ray of the chest showed a moderate increase in trunk markings throughout the midlung field on the right side, and some thickening of the apical pleura on both sides. Radiologic examination of the gastrointestinal tract disclosed considerable spasm of the stomach and a deformity of the duodenum suggestive of ulcer. Cholecystogram disclosed an angular deformity of the gall-bladder which was interpreted as due to pericholecystic adhesions. The cephalin flocculation test was + 1. The oral hippuric acid test revealed 1.9 gm./475 c.c. of urine. The electrocardiogram showed a slight slurring of the QRS complex. The basal metabolic rate was + 32.

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Repeated blood counts disclosed a continuous slight hypochromic anemia, and normal values for the white cells in the differential count except for 9 per cent eosinophiles on one occasion. Serum agglutination tests for *E. typhosus, E. paratyphosus* and *B. abortus* were negative. A test for occult blood in the stool was negative. The results of a gastric analysis were normal.

The patient improved symptomatically on a regimen of frequent soft feedings, alkalis, and sedatives, although he developed a persistent low grade fever and was dyspneic on several occasions. Coarse râles accompanied by prolonged expiration were heard intermittently over both lung fields. He was discharged April 28 with a diagnosis of duodenal ulcer and bronchial asthma.

The patient was readmitted on May 4 complaining of severe epigastric pain, vomiting, and pain in the legs. There was localized epigastric tenderness without rigidity, and a positive bilateral Homan's sign. The patellar reflexes were absent.

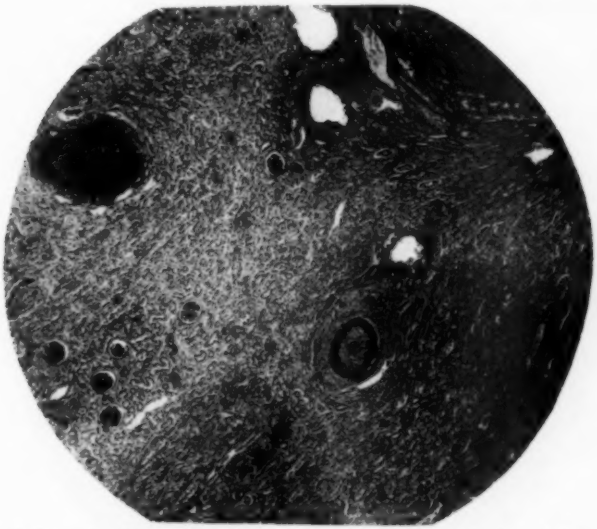

FIG. 1. Kidney showing two large vessels occluded by thrombosis and inflammatory reaction. × 20

The heart and lungs were normal on physical examination. The blood pressure was 160 mm. Hg systolic and 85 mm. diastolic. The temperature was 100° F., the pulse rate was 94 per minute, and the respirations were 22 per minute. Repeated blood studies showed a persistent moderate hypochromic anemia with a white blood cell count of 7,000 to 8,000 per cu. mm. The differential blood smear on admission disclosed 85 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes, and 3 per cent eosinophiles. A blood culture and examinations of the sputum for tubercle bacilli were negative. The serum amylase was 4 units (Winslow). Repeated urinalyses were noncontributory. The epigastric pain and vomiting persisted and were associated with a continuous remittent fever to 101° and 102° F. The pain in the legs became more severe and at times skin anesthesia of both legs existed. A skin test with an antigen of *Trichinella spiralis* was negative. A diagnosis of thrombophlebitis

was made and bilateral femoral vein ligation was performed on May 13. Following the operation the pain in the legs persisted, and the patient complained of numbness of the hands and left arm. On May 21, small subcutaneous nodulations were noted along the flexor surface of the left forearm, and several days later small crusted erythematous skin lesions were seen on the arms. At this time the diagnoses of lupus erythematosus, Boeck's sarcoid, and periarteritis nodosa were entertained but lacked substantiation. Roentgenographic examinations of the chest, abdomen, and lumbosacral spine were not significant.

On May 28, an exploratory laparotomy was performed, following the sudden onset of severe right upper quadrant pain. The findings at operation consisted of focal areas of pancreatic necrosis, enlargement of periaortic lymph nodes, and a large retroperitoneal hemorrhage on the right. The hematoma extended from the duodenum to the lateral abdominal wall and from the under surface of the liver to the right iliac artery. The gall-bladder was enlarged, but contained no calculi. Cholecystectomy was performed.

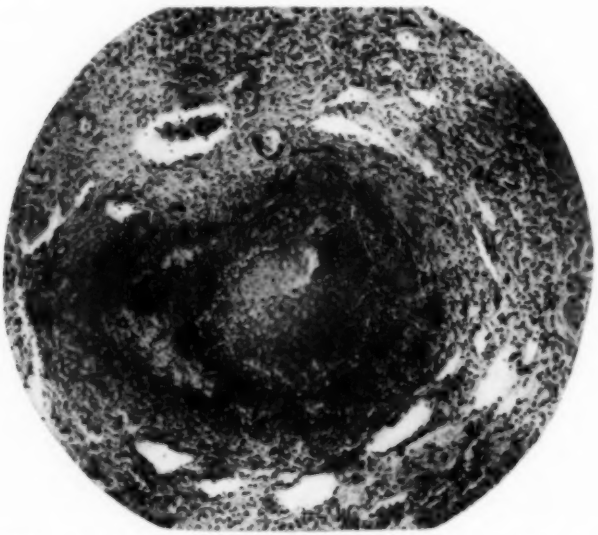

FIG. 2. Kidney showing thrombosis and necrosis of the vessel appearing to the left in figure 1. ×65.

Following the operation the patient complained of numbness and pain in the hands and legs, had several attacks of dyspnea which were relieved by adrenalin, and vomited frequently. His condition rapidly deteriorated and he died on May 31, approximately two months following his first admission.

Postmortem Examination. The autopsy was performed three hours after death. There was notable pallor of the oral mucosa, and moderate abdominal distention. There was a recent right rectus surgical incision from which a small amount of bloody fluid could be expressed. Approximately 50 c.c. of clear, straw-colored fluid were present in each pleural cavity, and the upper lobe of the left lung was adherent anteriorly by numerous fibrous adhesions. The lower lobes of both lungs were mod-

erately congested. The heart was grossly normal. There was extensive atheromatous degeneration of the aortic intima, with scattered areas of ulceration. The abdominal cavity contained an estimated 75 c.c. of serous fluid. There was slight gaseous distention of the intestines. No intrinsic lesions of the gastrointestinal tract were noted.

The liver was enlarged and weighed 2,190 gm. On section the cut surface presented the typical "nutmeg" appearance of passive congestion. In the dome of the left lobe, 2 cm. beneath the capsular surface, there was a spherical hematoma which measured 1.5 cm. in diameter. Near the hepatic hilus there was a pale, softened necrotic area of infarction which measured 1 cm. in its greatest dimension. The gallbladder contained a small amount of thick, dark green viscid bile and communicated with the surgical incision in the anterior abdominal wall. The spleen weighed 225 gm.; its parenchyma was friable, congested, and dark red in color. Numerous irregular chalky areas of fat necrosis were distributed throughout the pancreas which was bound to surrounding structures by fibrous adhesions.

Both kidneys were completely imbedded in massive, gelatinous, subcapsular blood clots. The renal capsules were intact, and had been dissected from the underlying parenchyma by hemorrhage. On the right the subcapsular hemorrhage communicated directly with a hematoma in the substance of the kidney. The cut surface of both kidneys revealed numerous hemorrhagic areas which measured from .5 to 1 cm. in diameter. The cortices were thin, and there was moderate blunting of the calyces. No communication existed between the two perirenal hematomas. No gross lesions were seen in either ureter. The bladder wall was somewhat thickened and edematous, and the prostate was nodular. The adrenal glands were situated at the superior aspect of the perirenal hematomas, and were grossly normal in appearance.

Microscopic Examination. Microscopic sections disclosed widespread vascular lesions of an inflammatory nature, involving the thyroid, aorta, small intestine, liver, spleen, pancreas, kidney, adrenals, and prostate. The lesions were most extensive in the liver, pancreas, kidneys, and adrenals. These organs presented an extensive, widespread, acute and chronic arteritis, in all stages of development. Frequently the arterial walls were involved in an acute necrotizing process, with a heavy infiltration of polymorphonuclear leukocytes in the adventitia. In other vessels, all layers were infiltrated with both acute and chronic inflammatory cells, including numerous eosinophiles. Other vessels were nodular, thickened and fibrous, and narrowing or complete occlusion was observed in many. In all of the organs thus affected there were large areas of infarction and of interstitial hemorrhage, with resulting destruction of the parenchyma.

Comment

In spite of the fact that various agents have at one time or another been incriminated, the cause of periarteritis nodosa is unknown. The investigations of Rich, [11, 12] and Rich and Gregory,[13] who in 1943 produced the lesion experimentally in rabbits by the injection of horse serum, constitute experimental evidence that periarteritis nodosa is a manifestation of the hypersensitive state, with the arteries reacting as the so-called "shock organ," and indicate that a wide variety of substances may play an antigenic rôle in the human.

In consideration of the allergic concept, the coexistence of bronchial asthma and periarteritis nodosa, as observed in this and other reported cases,[14, 15] may be more than coincidental. Whether or not a relationship exists between potential antigenic factors in the two diseases is a matter of conjecture.

The pathogenesis of the perirenal hemorrhage in this case was established by the demonstration at autopsy of a direct communication between the parenchymal and subcapsular hematomas, and by the intact renal capsules. The necrotizing

process in the renal arteries resulted in rupture of the vascular wall, dissecting interstitial hemorrhage, and ultimate perforation into the subcapsular space.

Summary

A case of periarteritis nodosa, terminating with massive bilateral perirenal hemorrhage, is presented.

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EDITORIAL

THE EXOERYTHROCYTIC CYCLE IN MALARIA

WHEN a susceptible subject is bitten by mosquitoes infected with malaria and containing sporozoites in their salivary glands, no symptoms appear until after an incubation period of about 10 days. With or slightly before the development of clinical symptoms, parasites first are found in the blood in demonstrable numbers. Until recently there were no direct observations of the parasites during the interval between inoculation and the appearance of parasites in the blood; and their location and activities have been a matter of speculation.

Schaudinn (1903) reported that after an infecting bite the sporozoites quite promptly penetrated into the red corpuscles, and he regarded the incubation period merely as the time required for the parasites to increase in number sufficiently to become demonstrable and excite clinical symptoms. His observation or assertion was never reliably confirmed, and there is much indirect evidence to contradict it.

It has been shown by a number of observers that if sporozoites are injected subcutaneously and the tissue at the site of injection is excised after a short interval, they can be demonstrated in this tissue, and if this is inoculated into a susceptible subject, the latter will become infected. Excision of the area, however, does not protect the first subject from infection; some sporozoites quickly escape into distant portions of the body, presumably through the blood stream. If a substantial volume of blood is withdrawn shortly (within about 20 minutes) after the inoculation or infecting bite and transfused into another subject, the latter will develop malaria. Within an hour or two at the most, however, the blood loses its infectivity and does not regain it until after an interval of usually about eight days. Even a massive inoculation of sporozoites does not materially shorten this interval.

During this period the parasites must be undergoing development and multiplication, and since they are not in the blood the process must occur in the tissues, presumably in the tissue cells. This has long been known to be the case in infections with *Haemoproteus*, an allied genus of parasites of birds.

Among the first to formulate this theory clearly and follow it up systematically were James and Tate, who in 1937 and 1938 [1] reported a study of hens infected with *Plasmodium gallinaceum*. They described nonpigmented parasites in the endothelial cells of the capillaries, particularly in the spleen, liver, kidneys and brain. In the more advanced stages these resembled the segmenting schizonts in red cells except that they were much larger, filling and distending the endothelial cells.

[1] JAMES, S. P., and TATE, P.: Exoerythrocytic schizogony in *Plasmodium gallinaceum* Brumpt, 1935, Parasitology, 1938, xxx, 128–139.

Their publication was preceded by that of Raffaele [2] who described similar structures in the endothelial cells of birds infected with *Plasmodium elongatum* and *P. relictum*. The earliest observation of this exoerythrocytic stage of the parasite, however, must probably be credited to Golgi who in 1893 in a study of birds infected with *P. immaculatum* described similar structures in the leukocytes and tissue cells which he interpreted as developing parasites. He also believed that this finding explained the resistance of the infection to antimalarial drugs and the tendency to repeated relapses. This important observation was made too soon for its importance to be appreciated, and it was either discredited or forgotten for more than 40 years.

The observations of Raffaele and of James and Tate stimulated many further investigations, and the presence and development of parasites in the tissue (endothelial) cells have been amply confirmed for many species of avian malaria. As direct proof, however, that this constitutes the intermediate stage between the sporozoite and the erythrocytic stage of the parasite, the evidence is less convincing, and there are discrepancies which are still difficult to explain.

Although in the case of some species the exoerythrocytic parasites were fairly numerous and easily found, in others they were very sparse and demonstrable in only a few of the infected birds; and in still other species none could be found at all. Even in species of Plasmodium which yield many exoerythrocytic forms, the latter may not be demonstrable until parasites have appeared in the blood (as in *P. gallinaceum* infections in hens, James and Tate). These observers also reported that in chickens infected by inoculations of blood containing *P. gallinaceum* in the erythrocytic stage only (but no sporozoites), exoerythrocytic forms subsequently developed, although at a later period in the infection. Such observations led some investigators to conclude that the tissue phase represents an alternative cycle rather than a necessary antecedent stage of development. Many of these difficulties can be solved by the plausible assumption that parasites in the tissue phase may be quite sparse and yet suffice to establish an infection; or that their distribution in the organs affected may be spotty. Recent work on the whole tends to support this view. The extensive earlier literature has been reviewed by Huff and Coulston [3] and by Davey.[4]

Following their discovery in avian malaria, many attempts were made to demonstrate parasites in the tissue cells in the malarias of man and monkeys. Although several workers described intracellular structures which they regarded as parasites, this interpretation was not accepted by the majority of

[2] Raffaele, G.: Il doppio ciclo schizogonico di *Plasmodium elongatum*, Riv. di Malariol., 1936, xv, 309–317.

Ibid.: Presumibli forme iniziali di evoluzione di *Plasmodium relictum*, Ibid., 318–324.

[3] Huff, C. G., and Coulston, F.: The development of *Plasmodium gallinaceum* from sporozoite to erythrocytic trophozoite, Jr. Infect. Dis., 1944, lxxv, 231–249.

[4] Davey, D. G.: Concerning exoerythrocytic forms and the evidence for their existence in human malaria, Trans. Roy. Soc. Trop. Med. and Hyg., 1946, xl, 171–182.

investigators (reviewed by Angelini [5]). Indirect evidence supporting the hypothesis of a tissue phase in man is so strong, however, that many have expressly or tacitly assumed its existence. Particularly significant are the differences in the incubation period following inoculation of sporozoites and of blood containing the erythrocytic parasites, and in the response to antimalarial drugs. Although the incubation period following inoculation of sporozoites is relatively fixed (eight to 10 days), regardless of the size of the inoculum, after inoculation of blood it varies with the size of the dose, and it can virtually be abolished if the latter is sufficiently massive. It is easy to eliminate the parasites in the erythrocytic phase and cure (temporarily) an acute attack of malaria by any of the usual drugs (quinine, atabrine, chloroquine, paludrine), but none of these will protect from infection under natural conditions or prevent relapses in vivax or quartan malaria. (Pamaquine and pentaquine do possess this power, particularly if quinine is also administered.[6])

The failure of the earlier investigators to find the tissue phase of mammalian malaria was evidently due to their not searching assiduously in the right place, attention presumably being centered on the endothelial cells in which the avian parasites were found. It remained for Shortt and Garnham to demonstrate this phase of the parasites in the parenchymal cells of the liver, both in monkeys infected with *P. cynomolgi* [7] and in a human volunteer infected with *P. vivax*.[8] After these investigators had shown what to look for and where to find it, their observations were quickly confirmed by Hawking [9] and by Huff and Coulston.[10]

Shortt and Garnham [11] infected monkeys, chiefly *Macaca mulata*, by subjecting them to the bites of large numbers (over 500) of mosquitoes infected with *P. cynomolgi* and subsequently injecting the ground-up bodies of the mosquitoes into the same animal. In some cases they made repeated biopsies of the liver of the same animal; in others individual animals were sacrificed at varying intervals following inoculation, and many different organs were examined. Up to the fifth day after inoculation no parasites were found. In tissues obtained from the fifth to the tenth day, inclusive, after inoculation, nonpigmented parasites were found in the parenchymal cells of the liver

[5] Angelini, G.: Incertezza dei reperti di "forme esoeritocitiche" dei plasmodi della malaria umana nel midollo osseo, Riv. Parasitol., 1947, viii, 5–18.

[6] Editorial: Some specific antimalarial drugs, Ann. Int. Med., 1948, xxix, 746–751.

[7] Shortt, H. E., and Garnham, P. C. C.: Pre-erythrocytic stage in mammalian malaria parasites, Nature, 1948, clxi, 126.

[8] Shortt, H. E., Garnham, P. C. C., Covell, G., and Shute, P. G.: The pre-erythrocytic stage of human malaria, *Plasmodium vivax*, Brit. Med. Jr., 1948, i, 547.

[9] Hawking, F., Perry, W. L. M., and Thurston, J. P.: Tissue forms of a malaria parasite, *Plasmodium cynomolgi*, Lancet, 1948, i, 783–789.

[10] Huff, C. G., and Coulston, F.: Symposium on exoerythrocytic forms of malaria parasites. II. Search for pre-erythrocytic stages of *Plasmodium vivax* and of *P. cynomolgi*, Jr. Parasitol., 1948, xxxiv, 264–274.

[11] Shortt, H. E., and Garnham, P. C. C.: The pre-erythrocytic development of *Plasmodium cynomolgi* and *Plasmodium vivax*, Trans. Roy. Soc. Trop. Med. and Hyg., 1948, xli, 785–795.

and thus far in no other tissue. These in general resembled the mature schizonts of the erythrocytic cycle, but they were larger and contained many more merozoites. The parasite on the fifth day was described as about 10.5 micra in diameter, with about 50 chromatin masses. These enlarged progressively until on the tenth day they measured 35 to 45 micra, distending the liver cell, and contained over 1000 minute merozoites. At this stage ruptured parasites were observed, from which the merozoites penetrated into the tissues and many undoubtedly entered the blood. Some were engulfed by phagocytes which collected in the tissues following rupture of the schizont. Whether some merozoites enter and infect other liver cells is not known in the case of mammalian malaria, although there is good evidence that this occurs in some types of avian malaria. Two types, micromerozoites and macromerozoites, have been described, one infecting the circulating erythrocytes, the other the endothelial cells, thus maintaining the tissue cycle. No such differentiation of merozoites has been reported in mammalian malaria.

Shortt and Garnham observed similar parasites in the liver cells of a human volunteer seven days after a heavy inoculation with sporozoites of *P. vivax*.

There is no direct evidence as to the life cycle of the parasite between the sporozoite and the schizonts observed in the liver cells on the fifth day. Shortt and Garnham believe that each sporozoite gives rise to a single schizont, but the possibility of an intermediate generation has not been positively excluded.

Shortt and Garnham[12] have obtained some evidence in support of the hypothesis that the parasites causing the late relapses are derived from those in the tissue phase. In one monkey infected with *P. cynomolgi* and examined by means of a liver biopsy after a clinical remission of one month, two parasites were found in the liver cells (but only after a survey of 412 histological sections). The following day the animal suffered a clinical relapse, and organisms reappeared in the blood.

It is not known whether merozoites derived from erythrocytic schizonts can enter liver cells and thus maintain the tissue cycle in mammalian malaria. This has been demonstrated in certain of the avian malarias.

These observations also throw some light on the scope of the immunity in malaria. The human volunteer was a psychotic patient who had been given malaria for therapeutic purposes 22½ months before by inoculation of blood containing the same strain of *P. vivax*. He did not develop clinical malaria following the inoculation with sporozoites. The immunity produced by his previous malaria, therefore, sufficed to suppress the erythrocytic cycle and protect him from a clinical attack, although it did not destroy the sporozoites nor prevent the development of the parasites in the tissue phase.

[12] Shortt, H. E., and Garnham, P. C. C.: Demonstration of a persisting exo-erythrocytic cycle in *Plasmodium cynomolgi* and its bearing on the production of relapses, Brit. Med. Jr., 1948, i, 1225–1228.

It should be noted that the dose of sporozoites inoculated in these experiments was collosal as compared with the number presumably introduced by the bite of one or a few infected mosquitoes under natural conditions. If a sporozoite gives rise only to a single exoerythrocytic schizont, the number of the latter would probably be so sparse in such material that a direct search would be extremely tedious at best and might well be fruitless. Inoculation experiments are not helpful for this purpose. The disease in mammals can not be conveyed by inoculations of hepatic tissue containing only exoerythrocytic parasites, although the reverse is true of avian malaria.

There seems to be no reasonable doubt as to the validity of these observations, although much remains to be learned regarding this phase of the life cycle of the malaria parasite. The scientific importance of these facts is obvious. From the practical standpoint their chief immediate importance is perhaps to give a reasonable explanation for the varying effect of specific drugs on the parasite at different stages of the infection, as well as for the late relapses. They should aid in devising logical and more effective measures of treatment.

P. W. C.

REVIEWS

A Course in Practical Therapeutics. By MARTIN EMIL REHFUSS, M.D., F.A.C.P., Professor of Clinical Medicine and Sutherland M. Prevost Lecturer in Therapeutics, The Jefferson Medical College, Philadelphia; Attending Physician, The Jefferson Medical College Hospital, Philadelphia; F. KENNETH ALBRECHT, M.D., formerly Clinical Director U. S. Marine Hospital, Baltimore, Md., and Co-director Division of Tuberculosis Control, Kansas State Department of Health; and ALISON HOWE-PRICE, A.B., M.D., Asst. Professor of Medicine, The Jefferson Medical College, Philadelphia; Asst. Physician to The Jefferson Medical College Hospital, Philadelphia; and a group of ten collaborating contributors. 824 pages; 22 × 29 cm. with 70 plates, 1 figure, 5 tables and 2 charts. The Williams and Wilkins Co., Baltimore, Md. 1948. Price $15.00.

This bulky comprehensive treatise is almost encyclopedic in its scope. It encompasses material assembled in teaching therapeutics to students at the Jefferson Medical College. The material is divided into four sections. The first consists of a brief outline of general therapeutic principles in which planning, prescription writing, dietary principles, nursing problems and the contents of the physician's bag are discussed in a concise and most practical manner. Section two deals with symptomatic therapy. In this section a symptom—such as, for example, vertigo—is briefly discussed and a list of causes given, followed by treatment. Instructive plates prepared by sketching essential information in diagrammatic forms on outlines of the human body, organ or anatomical area aid materially in visualizing the material presented. The third section deals with the treatment of specific disorders and comprises the bulk of the book. Each condition or disease is briefly described and detailed therapy given. Specific instructions are given for each therapeutic step recommended. The illustrations in this section are also most instructive. Section four deals with special treatment employed in eye, ear, nose, throat, skin and other special fields and is written mainly by collaborators chosen for their skill in the special field. This material is presented in a concise, readily available manner. It should prove most helpful to the general physician.

The field of therapeutics is covered in a thorough and instructive manner. Especially valuable is the plan outline of therapy followed by the details of procedures. The choice of therapeutic agents and technics is good and where several methods of treatment are available, they are also listed. This book supplies the need which has existed for a concisely written, yet comprehensive and practical converage of the field of therapeutics.

D. G. FRIEND

An Elementary Atlas of Cardiography. By H. WALLACE-JONES, M.D., M.Sc., F.R.C.P.; E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P.; and E. L. RUBIN, M.D., F.F.R., D.M.R.E. 108 pages; 14.5 × 23 cm. Williams and Wilkins Co., Baltimore. 1948. Price, $3.00.

This little book, written by members of the staff of the Royal Liverpool United Hospital, is intended to provide the medical student with a set of representative electrocardiograms and cardiac roentgenograms, to serve as an atlas, with a minimum of descriptive text. The text is too brief to present the subject adequately for students, and the illustrations too few to be of any great use as an atlas. Precordial leads are

referred to but briefly in the text, and appear in only a few of the illustrations. The section on cardiac radiology is generally better than that on electrocardiography.

The volume seems to fall short of its goal of supplying the needs of the medical student in this specialized field.

S. S.

Hope in Heart Disease: The Story of Louis Faugères Bishop, M.D. By RUTH V. BENNETT. 307 pages; 15 × 21 cm. Dorrance and Company, Philadelphia. 1948. Price, $3.00.

This is a biography of Louis Faugères Bishop, American pioneer in diseases of the heart. In the first decade of the 20th century Mackenzie had firmly established clinical cardiology in Britain, practical electrocardiography had been developed in Holland by Einthoven, and the value of roentgen-rays in cardiac diagnosis had been recognized in Germany by Groedel. In America these steps of progress were not yet appreciated. It was at this time that Bishop, in the face of criticism and in defiance of accepted standards, dared to call himself a "heart specialist." A little later (1915) he was one of the founders and original Fellows of the American College of Physicians. But his greatest achievement, his biographer states, was his success as an evangelist preaching the gospel of hope for those with heart disease.

From an intimate knowledge of Dr. Bishop's life work, the author treats her subject with great sympathy. A brief sketch of his antecedents is followed by a chronological treatment of his life—through schooldays, first struggles in practice, through the throes of establishing his specialty, to the mature physician whose doctrine changed the lives of so many cardiac sufferers. Each stage is amply illustrated with extracts from the doctor's own abundant writings. A list of Dr. Bishop's publications, seven books and nearly 200 papers, concludes the volume.

The author's style at times falls below the dignity of her subject. The lives of successful men, however, are always a profitable and stimulating study, and this biography may be enjoyed by medical men and laity alike.

H. J. L. M.

The Ciba Collection of Medical Illustrations. By FRANK H. METTER, M.D. 224 pages; 31.5 × 24 cm. Commissioned and published by Ciba Pharmaceutical Products Inc., Summit, New Jersey. 1948. Price, $6.50.

This large, cloth bound collection of pathologic conditions is vividly and well illustrated, and the accompanying text is adequate to supplement the pictures. Text and pictures are divided into four main sections: I. The Lungs and Chest; II. The Gastrointestinal Tract; III. Male Reproductive Organs and Male and Female Mammary Glands; IV. Heart and Aorta. The approach is mainly anatomic, with some of the surgical and etiologic aspects presented. Anomalies such as those of mammary development and hermaphroditism are pictured and described. Each picture is a representation of the fresh cadaver rather than the preserved as is usual in many anatomic publications. Color exaggerations are well employed for accentuation. Most of the composite pictures show the gross pathology, accompanied by auxiliary color interpretations of the microscopic appearance and roentgenographic aspects of the disease. Injuries and their effect on the internal organs are considered in some detail in the text and vividly pictured in the illustrations.

The book can serve for quick reference to the surgical, pathologic, anatomic and roentgenographic aspects of disease and injury and their relation to each other. The art work as a whole is excellent.

C. D. C.

Maternity in Great Britain: A Survey of Social and Economic Aspects of Pregnancy and Childbirth. 252 pages; 14.5 × 22.5 cm. Oxford University Press, New York. 1948. Price, $4.00.

This objective survey of maternal and infant welfare is based on a questionnaire inquiry of 13,687 mothers in England, Wales and Scotland who gave birth to babies during a single week in March, 1946. The remodelling of health services in Britain and the marked fall in fertility since the 1870's were the primary stimulants in this effort to obtain detailed information on the social and economic aspects of childbearing. The inquiries were carried out by health visitors in the normal course of their routine duties. The principal questions investigated were the availability of maternity services to different social classes in different parts of the country, the use made of these services, their effectiveness in educating mothers and reducing mortality and morbidity among mothers and infants, the need for domestic help during pregnancy and the puerperium, and the nature and extent of present-day expenditures on childbirth. The survey emphasizes the effect of regular antenatal supervision, begun early in pregnancy, on the incidence of prematurity and neonatal deaths and on the likelihood of establishing breast feeding. The need for more suitable clinic quarters for mothers seen on an appointment basis was quite apparent from the study. A review of the place of confinement in different areas suggests the need for a greater number of improved maternity hospitals and reveals that about 65 per cent of the home confinements in Britain are conducted by midwives. There follow interesting chapters on the relief of pain in childbirth and the value of postnatal examinations. Fifty-seven per cent of the babies had been taken to infant welfare centers before they were two months old. Again unsuitable and poorly located buildings were found in many places as in the case of the prenatal clinics. Overcrowding and staff shortages were discovered leading to hurried and inadequate consultations. Figures on the medical and non-medical costs of childbearing bring out the importance of this factor as an obstacle to childbearing which the provision of free confinement care under the National Health Service Act hopes to remove. Special aspects of the inquiry deal with the prevention of prematurity, infant feeding, working mothers, and the need for domestic help during the last weeks of pregnancy and the lying-in period. This survey is quite well done and is the first large-scale attempt to collect basic information with which to measure what maternity and child welfare services are available, how fully they are used and how far they fulfill the purposes for which they were designed.

M. A. N.

Management in Obstetrics. By ANDREW M. CLAYE. 186 pages; 19 × 12.5 cm. Oxford University Press, New York. 1948. Price, $3.75.

In the preface, the author, who is Professor of Obstetrics and Gynecology in the University of Leeds, advocates, for all physicians practicing obstetrics, postgraduate training leading to the degree of D.Obst., R.C.O.G. (an examination in obstetrics devised for the general practitioner). Physicians thus qualifying would not be obstetric specialists but would have a minimum of six months postgraduate experience in obstetrics. His book, dealing only with management in obstetrics, seems to be designed to aid those seeking this training.

Many of the 36 chapters are headed with appropriate quotations from literary classics which show the author's sense of humor. Important principles are emphasized in bold-face type in the text. There are only 17 illustrations, but obviously the book was intended to be used as an adjunct to one of the standard texts. In certain chapters, some operative technic is included. Some chapters include a bibliography which, in certain instances, is not too modern.

There are certain points of difference in principles of treatment in England and in the United States as exhibited in this book. Bed rest and progesterone only are advocated in the management of habitual abortion. The author believes antenatal supervision to be secondary in importance to the management of labor. Routine pelvic examination is not considered necessary, and internal clinical pelvimetry is done only if the head does not enter the pelvis at the thirty-sixth week. "There is small place for Cesarean section in the treatment of preeclampsia." The usual position for delivery is the left lateral position. Bipolar version and bag insertion are recommended in certain cases of transverse lie. In full medical induction the author gives up to 30 units of pituitary extract if necessary. In the repair of perineal tears and episiotomy skin clips or silkworm gut are used in the skin. Lateral episiotomy is recommended. For a tonic uterus, following delivery of the placenta, which does not respond to manual massage, the author advocates injecting ergometrine directly into the uterus through the abdominal wall.

In spite of these differences, this brief, practical and conservative book is a well written treatise on obstetric management which may be read with profit by the student and physician interested in obstetrics.

J. E. S.

BOOKS RECEIVED

Books received during March are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Atlas of Peripheral Nerve Injuries. By WILLIAM R. LYONS, Ph.D., Associate Professor of Anatomy, University of California Medical School, and BARNES WOODHALL, M.D., Professor of Neuro-surgery, Duke Medical School. 339 pages; 33 × 25 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $16.00.

Bone Marrow Biopsy: Haematology in the Light of Sternal Puncture. By S. J. LEITNER, M.D., Reader in Internal Medicine, University of Berne (Switzerland), etc.; English Translation Revised and Edited by C. J. C. BRITTON, M.D., Ch.B., D.P.H., Consulting Haematologist to the Prince of Wales's General Hospital, Tottenham, London, and Queen Mary's Hospital, Roehampton, etc., and E. NEUMARK, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P., Lecturer in Pathology, St. Mary's Hospital Medical School, London, etc. 433 pages; 25 ×16 cm. 1949. Grune & Stratton, Inc., New York. Price, $8.50.

The Ciba Collection of Medical Illustrations: A Compilation of Pathological and Anatomical Paintings. Prepared by FRANK H. NETTER, M.D. 224 pages; 31.5 × 24 cm. 1948. Commissioned and published by Ciba Pharmaceutical Products, Inc., Summit, N. J. Price, $6.50.

Current Therapy, 1949: Latest Approved Methods of Treatment for the Practicing Physician. HOWARD F. CONN, M.D., Editor; Consulting Editors, M. EDWARD DAVIS, VINCENT J. DERBES, GARFIELD G. DUNCAN, HUGH J. JEWETT, WILLIAM J. KERR, PERRIN H. LONG, H. HOUSTON MERRITT, PAUL A. O'LEARY, WALTER L. PALMER, HOBART A. REIMANN, CYRUS C. STURGIS, and ROBERT H. WILLIAMS. 672 pages; 28 × 20.5 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $10.00.

Hindu Medicine. By HENRY R. ZIMMER, Ph.D., Late Visiting Lecturer in Philosophy at Columbia University, etc.; Edited with a Foreword and Preface by LUDWIG EDELSTEIN, Ph.D. 203 pages; 20.5 × 14.5 cm. 1948. The Johns Hopkins Press, Baltimore. Price, $4.00.

An Introduction to Cardiology. By GEOFFREY BOURNE, M.D., F.R.C.P., Physician and Physician in Charge of the Cardiological Department, St. Bartholomew's Hospital. 264 pages; 22 × 14.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $4.50.

Practical Aspects of Thyroid Disease. By GEORGE CRILE, JR., M.D., F.A.C.S., Department of Surgery, Cleveland Clinic. 355 pages; 20.5 × 14 cm. 1949. W. B. Saunders Company, Philadelphia. Price, $6.00.

The Rh Blood Groups and Their Clinical Effects—Medical Research Council Memorandum No. 19. By P. L. MOLLISON, A. E. MOURANT and R. R. RACE. 74 pages; 24.5 × 15.5 cm. (paper-bound). 1948—Revised and Reprinted, November, 1948. His Majesty's Stationery Office, London. Price, 1 s. 6 d. net.

The Treatment of Pneumococcic Pneumonia in the Adult. By MORRIS F. COLLEN, M.D., Director, Department of Medicine, Permanente Foundation Hospital, Oakland, California. 166 pages; 23.5 × 15.5 cm. 1948. Permanente Foundation, Oakland, California. Price, $3.00.

COLLEGE NEWS NOTES

The New York Annual Session

The Thirtieth Annual Session of the American College of Physicians was conducted at the Waldorf-Astoria Hotel in New York City, March 28 to April 1, inclusive, 1949, under the Presidency of Dr. Walter W. Palmer, F.A.C.P., and the General Chairmanship of Dr. Franklin M. Hanger, F.A.C.P., both of New York City, with the very able assistance of numerous committees and local Fellows.

The program was marked by the excellence of the presentations and the wide field covered. Numerous new features were introduced into the program, such as the holding of certain clinics and pathological conferences at the Headquarters Hotel rather than requiring the physicians to travel long distances to the hospitals. This plan proved popular among the attendants and profitable to the institutions because their programs at the hotel were in every instance attended to capacity—more so than in the case of several of the clinics held in hospitals. The transport of ambulant patients to these clinics presented no undue problem and well justified the plan.

The Annual Convocation was conducted with marked dignity. Fellowships were conferred upon 255 physicians coming from various parts of North America. Masterships, in recognition of personal character, positions of influence, or eminence in the art of practice, or for attainments in medical research, were conferred upon Dr. James J. Waring, Denver, Colo., Dr. Elliott P. Joslin, Boston, Mass., Dr. Jonathan C. Meakins, Montreal, Que., and Dr. Virgil P. Sydenstricker, Augusta, Ga. The John Phillips Memorial Medal and Award was conferred upon Dr. Edwin B. Astwood, Boston, Mass., in recognition of his accomplishments in research in the field of hyperthyroidism. The James D. Bruce Memorial Medal and Award was conferred upon Dr. Stanhope Bayne-Jones, of New York, for his accomplishments in the field of preventive medicine, and the Alfred Stengel Memorial Diploma and Award was conferred on Dr. James J. Waring, of Denver, in recognition of his great service to the College in the past, his pioneering in the art of physical diagnosis, his work as a medical educator, clinical investigator and physician. Also at the Convocation the awarding of seven Research Fellowships by the College was announced, the recipients being Dr. John C. Laidlaw (Alfred Stengel Research Fellow), Dr. Stefan S. Fajans, Dr. Horace W. Gerarde, Dr. James Metcalfe, Dr. Samuel Moore Peacock, Jr., Dr. Jack L. Strominger and Dr. Edgar Woody, Jr. The Presidential Address was delivered by Dr. Walter W. Palmer, of New York City, and the Annual Convocational Lecture was presented by Dr. Henry Allen Moe, Secretary-General of The John Simon Guggenheim Memorial Foundation, of New York.

The Annual Banquet of the College was a brilliant affair, filling the Grand Ballroom of the Waldorf-Astoria Hotel. David Lilienthal, Chairman of the Atomic Energy Commission, Washington, D. C., gave the address of the day, "The Brighter Side of the Atom."

The attendance at this Annual Session of the College far exceeded that of any previous Meeting in the history of the College, there being a gross registration of 5,627, of whom 2,486 were members of the College, 1,471 were non-member physicians, 38 were guest non-physicians, 665 were exhibitors and 967 were ladies, wives of attending physicians. The largest gross registration at any previous Meeting of the College was at the Chicago Session in 1947 when the total was 4,410, made up of 1,694 members, 1,382 guest physicians, 70 guest non-physicians, 137 medical students, 518 exhibitors and 609 ladies. Physicians were in attendance from all states of the United States, the Canal Zone, Puerto Rico, Hawaii, Argentina, Australia, Canada, Colombia, Cuba, England, Finland, Germany, India, Italy, the Netherlands and the Philippines.

It should be noted that at the New York Session medical students were not admitted because of inadequate facilities. It is regretted that many members were unable to obtain seats at several of the various functions due to the exceedingly large attendance. This has resulted in the Board of Regents and the Board of Governors instituting a plan to reduce the attendance of non-members in the future. Hereafter, non-members will have to be sponsored by members of the College in advance of the Meeting and the non-member registration fee will be increased from $15.00 to $25.00. The College does not wish to withhold the benefits of its Meetings to interested physicians, but necessity dictates some plan by which members of the College shall be accommodated first. Many cities are no longer able to accommodate the Annual Session of the College, and, thus, restrictive measures must be taken.

The Technical Exhibit of the 1949 Annual Session was the largest and offered the most varied interest of any to the members and guests of the College. There were some 99 firms represented, occupying 122 booths.

The Editor will begin the publication of papers from the Annual Session in the ANNALS OF INTERNAL MEDICINE with the June issue, and various presentations from the New York Session will follow each succeeding month.

The Thirty-First Annual Session will be held in Boston, Mass., April 17–21, 1950, with Hotel Headquarters at the Hotel Statler and the Hotel Copley Plaza, and with General Headquarters for the Meeting in the Mechanics Hall. It is confidently expected that facilities will be wholly adequate to accommodate all members of the College, both in hotel rooms and in all of the meetings. Dr. Reginald Fitz, F.A.C.P., President of the College, 319 Longwood Ave., Boston 15, Mass., will be in charge of the program of Morning Lectures and General Sessions. Dr. Chester S. Keefer, 65 E. Newton St., Boston, Mass., has been appointed by the Board of Regents as the General Chairman and will be in charge of local arrangements and the program of Panel Discussions and Clinics, as well as entertainment features.

The Thirty-Second Annual Session will be held at St. Louis, Mo., April 9–13, 1951.

ELECTIONS TO MEMBERSHIP, MARCH 27, 1949

The Board of Regents of the American College of Physicians met in New York City on March 27, 1949. The following candidates were elected as Fellows or Associates of the American College of Physicians. Those elected to Fellowship are indicated in full capital letters; those to Associateship, in capital letters and lower case.

Alfred J. Ackerman, M.C., U. S. Army
HORST ALBERT AGERTY, Philadelphia, Pa.
Edwin Carter Albright, Madison, Wis.
F(REDERICK) GERARD ALLISON, Winnipeg, Man., Can.
LEE ANDERSON, San Jose, Calif.
HORACE ALFRED ANDERSON, Tacoma, Wash.
Earl Henry Antes, Evansville, Ind.
DANA WINSLOW ATCHLEY, New York, N. Y.
Morris Axelrod, Brooklyn, N. Y.

CHARLES CABELL BAILEY, Newton, Mass.
Seymour Samuel Balkin, Jamaica, N. Y. (V.A.)
PAUL SHIRMER BARKER, Ann Arbor, Mich.
Benjamin Baron, New York, N. Y.
William Henry Bates, Cottonwood, Ariz.
D. R. Bedford, Topeka, Kans.

PAUL BRUCE BEESON, Atlanta, Ga.
William Henry Beierwaltes, Ann Arbor, Mich.
GORDON IRVING BELL, Edmonton, Alta., Can.
WILLIAM OSLER BENENSON, Flushing, N. Y.
ADOLPH R. BERGER, New York, N. Y.
Morton Semur Berk, Newton Center, Mass.
Henry Scholten Bernet, Springfield, Ill.
MAXWELL RUFUS BERRY, Atlanta, Ga.
Howard Richard Bierman, San Francisco, Calif.
JOHN ALFRED BOONE, Charleston, S. C.
SIEGBERT BORNSTEIN, Oteen, N. C. (V.A.)
William Whelan Bourke, Knoxville, Iowa (V.A.)
Samuel Huntington Boyer, Jr., Duluth, Minn.
Joachim O. W. Brabander, Montreal, Que., Can.
Vernon C. Branham, Silver Spring, Md. (V.A.)
EARL WINFREY BRIAN, Raleigh, N. C.
Irving Benjamin Brick, Washington, D. C.
FRANCIS STAPLES BRIEN, London, Ont., Can.
Henry Jerome Brock, Buffalo, N. Y.
Stephen William Brouwer, Clifton Springs, N. Y.
GEORGE RAYMOND BROW, Montreal, Que., Can.
Charles Howard Brown, Cleveland, Ohio
George Emerson Brown, Twin Falls, Idaho
WILBERT HURST BROWN, Toronto, Ont., Can.
JOHN SYMONDS LYON BROWNE, Montreal, Que., Can.
JAMES STEPHEN BROWNING, Indianapolis, Ind.
BERT MONTELL BULLINGTON, Saginaw, Mich.
Paul Axtell Bunn, Syracuse, N. Y.
John James Bunting, Houston, Tex.
PAUL ARTHUR BURGESON, Warsaw, N. Y.
Louis Emanuel Burns, Newport, R. I.

HAYES WOODROW CALDWELL, Phoenix, Ariz.
J(ASPER) LAMAR CALLAWAY, Durham, N. C.
PAUL BROOMHALL CAMERON, Pryor, Okla.
Richard Gardner Canfield, Pittsburgh, Pa.
JESSE FLOYD CANNON, Salt Lake City, Utah
Max Caplan, Meriden, Conn.
Paul Simon Caplan, Pittsburgh, Pa.
Henry Ashley Carr, New York, N. Y.
Thomas Lyle Carr, Iowa City, Iowa
LEON DELWIN CARSON, M.C., U. S. Navy
Robert Johnson Catlin, St. Albans, Vt.
ORREN DANIEL CHAPMAN, Syracuse, N. Y.
GARNETT CHENEY, San Francisco, Calif.
LOUIS JOSEPH CHESKIN, Newark, N. J.
Herbert Lee Clay, Jr., Louisville, Ky.
HENRY PLETCHER CLOSE, Coatesville, Pa. (V.A.)
SAMUEL E. COHEN, Elmira, N. Y.
Merchant William Colgin, Waco, Tex.
STUART RICHARDSON COMBS, Terre Haute, Ind.
WILLIAM V. CONN, Greensburg, Pa.
James Frederick Conner, Rochester, N. Y.

R(EASON) LOUIS COPE, Houston, Tex.
WALTER ALLEN CRIST, Camden, N. J.
Gary Arnold Cronk, Syracuse, N. Y.
ROBERT WILLIAM CURRIE, La Fayette, Ind.

Virgil Clayton Daniels, Jr., St. Petersburg, Fla.
HAL DAVIS, Roanoke, Va.
Richard Barre Davis, Bennington, Vt.
William Duncan Davis, Jr., New Orleans, La.
A(lonzo) Ray Dawson, Richmond, Va. (V.A.)
JOHN ENGLISH DEITRICK, New York, N. Y.
C(AMILLE) JOSEPH DeLOR, Columbus, Ohio
John D. DePersio, Oak Ridge, Tenn.
LEWIS DEXTER, Boston, Mass.
Henry David Diamond, New York, N. Y.
Morris Marcus Dick, Coral Gables, Fla. (V.A.)
ROBERT CLARK DICKSON, Toronto, Ont., Can.
EDMOND KING DOAK, Houston, Tex.
Kenneth Thomas Donaldson, New York, N. Y.
Ferdinand Donath, Cincinnati, Ohio
Charles Kendall Donegan, St. Petersburg, Fla.
Isadore Nathan Dubin, Memphis, Tenn.
Wolcott Balestier Dunham, Memphis, Tenn. (V.A.)

J(OSEPH) RUSSELL ELKINTON, Philadelphia, Pa.
GEORGE FREDERICK ELLINGER, U. S. Public Health Service
ROBERT WILLIAM ELLIOTT, Alton, Ill.
Edwin Curtis Evans, Atlanta, Ga.
KENNETH AUSTIN EVELYN, Montreal, Que., Can.
DAVID WUEST EXLEY, Miami Beach, Fla.

David Earl Fader, Augusta, Ga. (V.A.)
Benjamin B. Faguet, San Diego, Calif.
PAUL STRIMPLE FANCHER, M. C., U. S. Army
Thomas Wohlsen Farmer, Dallas, Tex.
Samuel Feinstein, Ogdensburg, N. Y.
WILLIAM ANTHONY FEIRER, Narberth, Pa.
GEORGE KINGSLEY FENN, Beverly, Mass.
LUCIAN MINOR FERRIS, Vicksburg, Miss.
HARRY THOMAS FOLEY, II, Castle Shannon, Pa.
Paul Jones Fouts, Indianapolis, Ind.
NATHAN FRANK, Jersey City, N. J.
Jerome S. Frankel, Cleveland, Ohio
Myron A. Freilich, Zanesville, Ohio
HENRY FULLER, Lakeland, Fla.

Jacques Lester Gabrilove, New York, N. Y.
CHARLES LEON GASS, Sackville, N. B., Can.
WILLIAM IRVIN GEFTER, Philadelphia, Pa.
Henry Gibbons, III, San Francisco, Calif.
JOHN PAUL GIBSON, Abilene, Tex.
Elmer Wilhelm Gilbert, Alhambra, Calif.
ISADORE WILCHER GINSBURG, Philadelphia, Pa.
ROBERT EARLE GLENDY, Roanoke, Va.

DONALD LOCKHART GLENN, Urbana, Ill.
RUBIN LEONARD GOLD, San Francisco, Calif.
WALTER GOLDFARB, New York, N. Y.
ALLAN MICHEL GOLDMAN, New Orleans, La.
PHILIP GOLDSTEIN, New York, N. Y.
Samuel Zangwill Goodman, Los Angeles, Calif.
Arthur Gordon, Woodside, L. I., N. Y.
Maurice Gore, Chicago, Ill.
Warren Frederic Gorman, New York, N. Y.
M(ACK) LEONARD GOTTLIEB, New York, N. Y.
EDWIN MATTHEW GOYETTE, M.C., U. S. Army
John Joseph Grady, Lakewood, Ohio
Irving Graef, New York, N. Y.
Clyde Cornelius Greene, Jr., San Francisco, Calif.
GEORGE SMITH GRIER, III, Newport News, Va.
Peter Vincent Gugliuzza, Bellerose, N. Y.
Edward George Gullord, Montclair, N. J.

Woodhull Stanton Hall, Bennington, Vt.
Morton Hamburger, Cincinnati, Ohio
FREDERICK CARLYLE HAMILTON, Toronto, Ont., Can.
Ottis Eugene Hanes, Atlanta, Ga.
HANCE FRANCIS HANEY, Portland, Ore.
Irving John Hanssmann, Philippi, W. Va.
GEORGE THOMAS HARRELL, JR., Winston-Salem, N. C.
William Henry Harris, Jr., Richmond, Va.
Marlow Bristow Harrison, San Francisco, Calif.
Harold Ira Harvey, Berkeley, Calif.
JAMES PAISLEY HENDRIX, Durham, N. C.
George Carl Hennig, New York, N. Y.
JOHN SEVERY HIBBEN, Pasadena, Calif.
John Bamber Hickam, Durham, N. C.
Cotter Hirschberg, Denver, Colo.
Helena Hoelscher, South Euclid, Ohio
CLYDE WALLACE HOLLAND, Halifax, N. S., Can.
Daniel Holzman, Brookline, Mass. (V.A.)
SIBLEY WORTH HOOBLER, Ann Arbor, Mich.
HENRY HORN, New York, N. Y.
LEONARD HORN, Rochester, N. Y.
JOHN LINSCOTT HORNER, St. Louis, Mo.
Elmer Leaman Horst, Reading, Pa.
ROBERT MACLAY HOYNE, Urbana, Ill.
Byron James Hughes, Winnebago, Wis.
John Willis Hurst, Boston, Mass.
Lucile West Hutaff, Winston-Salem, N. C.
Howard Joseph Hutter, Huntington, N. Y.

Thomas Leonard Ippolito, Norwalk, Conn.
Sydney Israels, Winnipeg, Man., Can.

Ralph Franklin Jacox, Rochester, N. Y.
Charles Harold Jaimet, Hamilton, Ont., Can.
EDWARD RUPEN JANJIGIAN, Kingston, Pa. (V.A.)
Philip Borrello Johnson, New Orleans, La.

Robert Driscoll Johnson, Syracuse, N. Y.
FRANKLIN DAVIS JOHNSTON, Ann Arbor, Mich.
Leland Mann Johnston, Jackson, Tenn.
Ben(jamin) Calloway Jones, Jr., Alexandria, Va.
HORACE LEONARD JONES, JR., M.C., U. S. Navy
Franz Christian Jost, New York, N. Y.

Bernard Merle Kalstone, Shreveport, La.
Nolan Levi Kaltreider, Rochester, N. Y.
Harry Arnold Kaplan, Trenton, N. J.
ANTHONY MILOSH KASICH, New York, N. Y.
Benjamin Katzin, Torrington, Conn.
George Leonard Kauer, Jr., New York, N. Y.
JULIAN ROWE KAUFMAN, Augusta, Ga. (V.A.)
Gustav Grosvenor Kaufmann, Winchester, Mass.
JULIUS KAVEE, New York, N. Y.
CALVIN F. KAY, Philadelphia, Pa.
Emmett Leroy Kehoe, M.C., U. S. Army
AARON KEINIGSBERG, Chicago, Ill.
R(obert) Emmet Kelly, St. Louis, Mo.
Raymond William Kelso, Long Beach, Calif.
JAMES LeROY KIMBALL, Salt Lake City, Utah
ROBERT WILLIS KIMBRO, Cleburne, Tex.
ABRAHAM MORRIS KLEINMAN, Brooklyn, N. Y. (V.A.)
Nathan Schellenberg Kline, Lyons, N. J. (V.A.)
Melvin Karl Knight, Vancouver, Wash. (V.A.)
J. LESTER KOBACKER, Toledo, Ohio
Michael Francis Koszalka, Milwaukee, Wis. (V.A.)
CHARLES HYMAN KRAVITZ, Philadelphia, Pa.
Benjamin Earl Krentz, New York, N. Y.
JOHN JOSEPH KRYGIER, Portland, Ore.
RALPH HESS KUNSTADTER, Chicago, Ill.

Daniel Harvey Labby, Portland, Ore.
Morris Lattman, New York, N. Y. (V.A.)
Gerald O. Laxson, Knoxville, Iowa (V.A.)
NORMAN LEARNER, Philadelphia, Pa.
WILLIAM VINCENT LEARY, Rochester, Minn.
JOSEPH HOWARD LEE, Hamilton, Ont., Can.
Robert Edward Lee, Chicago, Ill.
ELFRED LLEWELLYN LEECH, Oneonta, N. Y.
Emanuel Levokove, Far Rockaway, N. Y.
HERMAN ABRAHAM LEVY, Chicago, Ill.
Bernard Irvin Lewis, Kingston, Ont., Can.
Claud Lewis, St. Cloud, Minn. (V.A.)
James Farrar Lewis, Columbus, Miss.
Jacob Lichstein, Hollywood, Calif.
Saul Lieb, Newark, N. J.
WILLIAM H. LONG, Fargo, N. D.
JOSEPH M. LUBITZ, Wood, Wis. (V.A.)
ARTHUR GEORGE LUECK, Des Moines, Iowa
JOSEPH AUGUSTINE LUNDY, Worcester, Mass.
Francis T. Lytle, Fargo, N. D.

Harry Pearce Maccubbin, Martinsburg, W. Va. (V.A.)
RANALD IAN MACDONALD, Toronto, Ont., Can.
THOMAS EMERY MACHELLA, Philadelphia, Pa.
Hector Hugh MacKinnon, Fredericton, N. B., Can.
JAMES MURDOCK MacMILLAN, Richmond, Va.
Edward I. Margaretten, Perth Amboy, N. J.
HAROLD HENRY MARQUIS, San Francisco, Calif.
GEORGE ELMER MARTIN, Pittsburgh, Pa.
Mary Elizabeth Martin, Billings, Mont.
Peter Herman Marvel, Northfield, N. J.
Wiley Roy Mason, Jr., Charlottesville, Va.
Frank Pelletreau Mathews, New Haven, Conn.
Eugene Francis McAuliffe, Milton, Mass.
William Earl McCullough, Jamaica, N. Y.
L(EWIS) TILLMAN McDANIEL, Boston, Mass.
Richard Donald McKenna, Montreal, Que., Can.
Jonathan Fayette Meakins, Montreal, Que., Can.
Lawrence Meyers, New York, N. Y.
HENRY MILLER, Providence, R. I.
Moore Anderson Mills, Seattle, Wash.
John Milne, Hanover, N. H.
Jacob Arthur Mishkin, Watertown, N. Y.
Earl Brewster Mitchell, Oakland, Calif.
John Adams Mitchell, Monaca, Pa.
FRANK THEODORE MOORE, Akron, Ohio
F(REDERICK) STANLEY MOREST, Kansas City, Mo.
PHILIP MORGENSTERN, Oteen, N. C. (V.A.)
MILTON HOWARD MORRIS, Far Rockaway, N. Y.
PAUL HARRY MORTON, M.C., U. S. Navy
Eli Rodin Movitt, Oakland, Calif. (V.A.)
WALDO BRIGGS MOYERS, Mt. Rainier, Md.
Fay Ballenger Murphey, Jr., Chattanooga, Tenn.
CLIFFORD KINNAIRD MURRAY, Ventnor, N. J.

RICHARD MARION NAY, Indianapolis, Ind.
Frederick Levering Neely, Atlanta, Ga.
MARSHALL GRANT NIMS, Denver, Colo.
Lewis Earle Nolan, Fairmont, W. Va.

THEODORE WRIGHT OPPEL, New York, N. Y.
Kermit Edward Osserman, New York, N. Y.

SIDNEY GREY PAGE, JR., Richmond, Va.
Eddy Davis Palmer, M.C., U. S. Army
RUSSELL ALFRED PALMER, Vancouver, B. C., Can.
Wesley Eugene Peltzer, Salt Lake City, Utah
CHARLES STEHMAN PENNYPACKER, Ardmore, Pa.
Lawrence Perlman, Chicago, Ill.
Hector Perrone, New York, N. Y.
Thomas Henry Phalen, Binghamton, N. Y.
FRANK VINCENT PICCIONE, Hazleton, Pa.
FRANK JAMES PIEKENBROCK, Dubuque, Iowa
Richard France Platzer, Clifton Springs, N. Y.
CLARK POSTON PRITCHETT, Columbus, Ohio
William Orgain Purdy, Des Moines, Iowa

THOMAS JAMES QUINTIN, Sherbrooke, Que., Can.

Emanuel Mortimer Rappaport, Jamaica, N. Y.
WELLFORD CLAIBORNE REED, Richmond, Va.
Robert Ladd Richards, Chester, Vt.
Edward Alton Ricketts, M.C., U. S. Army
SEYMOUR HAROLD RINZLER, New York, N. Y.
JOSEPH FRANKLIN ROBINSON, Wilkes-Barre, Pa.
David Edward Rodger, Regina, Sask., Can.
ARTHUR MERIAM ROGERS, Philadelphia, Pa.
Joseph Rogers, Boston, Mass.
JACK ROM, Detroit, Mich.
S(amuel) Allison Rose, Stamford, Conn.
Henry Norman Rosenberg, Brookline, Mass.
Rigby Clyde Roskelley, Chicago, Ill.
LEON ROSOVE, Santa Monica, Calif.
Karl Dean Rundell, Endicott, N. Y.
HAROLD EDMUND RYKERT, Toronto, Ont., Can.

JOSEPH FRANCIS SADUSK, JR., Washington, D. C.
Andres E. Salazar y Rivera, Santurce, P. R.
STUART SANGER, Tucson, Ariz.
Louis A. Sarrow, Far Rockaway, N. Y.
CHARLES LINWOOD SAVAGE, Waynesboro, Va.
James George Sawyer, Butte, Mont.
JOHN JOYCE SAYEN, Wynnewood, Pa.
Maurice William Sbertoli, Chicago, Ill.
Alvin Albert Schaye, New York, N. Y.
Samuel T. Schlamowitz, New York, N. Y.
Harold Otto Schneider, Salem, Ore.
Louis Schneider, Mt. Vernon, N. Y.
RALPH FREDERICK SCHNEIDER, New York, N. Y.
Robert Woodrow Schneider, Cleveland, Ohio
SAMUEL JACOB SCHNEIERSON, New York, N. Y.
Jacob Schott, Brooklyn, N. Y.
WILLIAM SCHULZE, Greenville, S. C.
Samuel Harold Schwartz, Plainfield, N. J.
Solomon Schwartz, Flushing, N. Y.
STEVEN OTTO SCHWARTZ, Chicago, Ill.
Virgil C. Scott, St. Louis, Mo.
William Craven Scott, Portland, Ore.
Joseph Shaiken, Milwaukee, Wis.
Edward Shapiro, Beverly Hills, Calif.
Morris Arnold Shapiro, Schenectady, N. Y.
Nathan Shapiro, Cincinnati, Ohio
Palmer Augustine Shelburne, Greensboro, N. C.
RALPH KENNETH SHIELDS, Bethlehem, Pa.
HARRISON JOHNSTON SHULL, Nashville, Tenn.
WENDELL ARTHUR SHULLENBERGER, Indianapolis, Ind.
Norman Morrison Shure, Beverly Hills, Calif.
Herbert Benjamin Silberner, Newark, N. J.
Benedict Skitarelic, Cumberland, Md.
Howard Bernard Slavin, Rochester, N. Y.
Maurice Jacob Small, Staten Island, N. Y. (V.A.)
Gerald Howard Smith, Colorado Springs, Colo.

HERMAN JOSEPH SMITH, Des Moines, Iowa
J(ohn) James Smith, New York, N. Y.
MARTIN DeFOREST SMITH, New York, N. Y.
William Weber Smith, Los Angeles, Calif.
Maurice Sones, Philadelphia, Pa.
SAMUEL HERMAN SPITZ, Brooklyn, N. Y.
HAROLD ERVIN STADLER, Indianapolis, Ind.
DALE COOK STAHLE, Harrisburg, Pa.
Isidore Stein, Brooklyn, N. Y.
Alfred Steiner, New York, N. Y.
VALENTINE FREDERICK STOCK, Toronto, Ont., Can.
Hugh Albert Stout, Oklahoma City, Okla.
Paul Theodore Strong, Tulsa, Okla.
James Baytop Stubbs, St. Louis, Mo.
LEON NATHANIEL SUSSMAN, New York, N. Y.
LESLIE WILLIAM SWANSON, Mason City, Iowa
William Porter Swisher, Evanston, Ill.

Theodore Joseph Talbot, Staten Island, N. Y.
Rosario Terranova, New York, N. Y.
Wildridge Clark Thompson, Jackson, Miss.
David Cushman Thurber, Rochester, N. Y.
ARTHUR MANDEL TUNICK, New York, N. Y.

ROBERT ADOLPH ULLMAN, Buffalo, N. Y.

HOWARD AMOS VAN AUKEN, M.C., U. S. Army
HOWARD SCOTT VanORDSTRAND, Shaker Heights, Ohio
RICHARD WILLIAM VILTER, Cincinnati, Ohio
Odon Francis von Werssowetz, Nashville, Tenn. (V.A.)
Gordon Stanley Voorhees, Leavenworth, Kans.

MAXIMILIAN WACHSTEIN, Brooklyn, N. Y.
Arnold Louis Wagner, Evanston, Ill.
Robert Tracy Walker, St. Johnsbury, Vt.
John Vogel Waller, New York, N. Y.
JAMES ALLAN WALTERS, Toronto, Ont., Can.
JOSEPH EDWARD WALTHER, Indianapolis, Ind.
George Fenton Warner, San Francisco, Calif.
GEORGE DAVIS WEICKHARDT, Washington, D. C.
James Irving Weimer, Pekin, Ill.
Harry Anthony Weiss, M.C., U. S. Navy
Louis Robert Weiss, Brookline, Mass. (V.A.)
Sidney C. Werner, New York, N. Y.
CHARLES HERMAN WHITE, Sumter, S. C.
PAUL LUKE WHITE, Austin, Tex.
ARNOLD HARRY WIDERMAN, Philadelphia, Pa.
John Carroll Wiggins, Jr., Winston-Salem, N. C.
KEITH JOHN ROY WIGHTMAN, Toronto, Ont., Can.
Seymour Karl Wilhelm, Detroit, Mich.
RAY DAVID WILLIAMS, St. Louis, Mo.
William Darrell Willis, M.C., U. S. Army
Donald Robert Wilson, Edmonton, Alta., Can.
SLOAN JACOB WILSON, Kansas City, Kans.

John R. Winston, Temple, Tex.
William Miles Witherspoon, Rochester, N. Y.
Abraham Wolbarsht, Brookline, Mass. (V.A.)
DONALD EUGENE WOOD, Indianapolis, Ind.
James Watson Woods, Durham, N. C.
Frederick Gaston Woodson, Norfolk, Va.
VICTOR FELSENTHAL WOOLF, New York, N. Y. (V.A.)
Joseph Franklin Worthen, Staten Island, N. Y.
DUWARD OLERA WRIGHT, Birmingham, Ala.
Richard Ellis Wunsch, Detroit, Mich.

Marion Twitty Yates, M.C., U. S. Navy
ANDREW YEOMANS, White River Junction, Vt. (V.A.)
Charles Lorenzo York, Jr., Decatur, Ill.
LAWRENCE EUGENE YOUNG, Rochester, N. Y.
Anton Stanley Yuskis, San Diego, Calif.

FREDERIC DAVID ZEMAN, New York, N. Y.
Boris Zemsky, Tucson, Ariz.
J(OSEPH) LaMONTE ZUNDELL, M.C., U. S. Navy

Alabama Members Planning Regional Meeting

Dr. E. Dice Lineberry, F.A.C.P., Governor for Alabama, conducted a luncheon meeting of the Masters, Fellows and Associates of the American College of Physicians who were in attendance at the Alabama State Medical Association Meeting at Montgomery, Ala., on April 20, and outlined the plans for a Regional Meeting of the College to be held at Birmingham in the Autumn. The Regional Meeting will include South Carolina, Georgia, Florida, Alabama and Cuba, the Alabama members acting as hosts.

Specialty Board Notices

The American Board of Pediatrics, Inc., John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Road, Rosemont, Pa. Written examinations will be held under local monitors on June 24, 1949, from 2 to 4 p.m. Oral examinations will be held at Cleveland, Ohio, September 16–18, 1949; at New York, October 21–23, 1949; and at Chicago, Ill., December 9–11, 1949.

The American Board of Psychiatry and Neurology, Inc., F. J. Braceland, M.D., Secretary-Treasurer, 102–2nd Avenue, S. W., Rochester, Minn. A special examination will be held in October at a place and on a date to be announced later. Applications for examination and requests for re-examination should be sent to the Secretary-Treasurer before June 15, 1949. This examination is in addition to the regular semi-annual examinations held in May and December.

Training School for Cardiovascular Investigators, Department of Physiology, School of Medicine, Western Reserve University, Cleveland, Ohio

A twelve months training course in the disciplines of cardiovascular research for a limited number of qualified individuals will be offered with the support both of the

American Heart Association and the National Heart Institute, U. S. Public Health Service. If the enrollment warrants, the course will begin July 1, 1949; otherwise Sept. 1, 1949. For details write: Dr. C. J. Wiggers, Director of the Department of Physiology, School of Medicine, Western Reserve University, Cleveland, Ohio.

The University of California Medical School (Medical Extension) announces a postgraduate course in the medical aspects of nuclear energy, August 29 through September 3, 1949 at the Medical Center, in San Francisco. Chairman of the course is Dr. Joseph G. Hamilton, Associate Professor of Experimental Medicine and Radiology, Associate Professor of Medical Physics, and Director of the Crocker Laboratory, University of California.

Fee for this course will be announced in the detailed program which will be mailed upon request addressed to: Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

University of Southern California Offers Full-Time, One-Year Postgraduate Courses

Dr. Edward C. Rosenow, Jr., F.A.C.P., Director, Extension Medical Education, University of Southern California School of Medicine, has announced the following courses to be given on a full-time basis for a period of one year, the courses being approved for graduate training and board certification:

Cardiology—Dr. George C. Griffith, F.A.C.P., Director.
Internal Medicine—Dr. Paul Starr, F.A.C.P., Director.
Dermatology—Dr. Maximilian E. Obermayer, Director.

Medical Literature Sorely Needed by Japanese Physicians

Medical officers in the U. S. Army report a severe shortage of medical literature for the use of the Japanese profession. The war left them in poor economic circumstances, and they cannot afford subscriptions to American journals except in rare instances. No medical literature reached Japan during the war years. A large number of Japanese doctors use the Army medical literature in the local libraries and are frequently seen to copy laboriously complete articles. Many of the American medical officers have given these Japanese doctors journals, drug house literature and other material, and have loaned them their own personal medical books.

The Deputy Surgeon General of the Army is anxious to assist in any manner possible to help supply medical literature. Colonel Francis W. Pruitt, (MC), USA, 49th Medical General Hospital, APO No. 1052, c/o Postmaster, San Francisco, Calif., is acting in an advisory capacity to the Tokyo Jikei-Kai School of Medicine and offers to be an intermediary between members of the College and some of the Japanese institutions and physicians for the distribution of any medical literature which American doctors wish to mail him. Using the above address, only domestic postage will be required.

OBITUARIES

COLONEL ALEXANDER T. COOPER (MC), U. S. ARMY, RETIRED

Colonel Alexander Taylor Cooper (MC), U. S. Army, Retired, died on January 2 of this year in San Juan, P. R., where he had made his home since retiring from active duty in 1940. Burial was in Arlington Cemetery.

Colonel Cooper was born in Yutan, Nebr., April 8, 1883. He attended Bellevue College, Bellevue, Nebr., and was graduated from the Medico-Chirurgical College of Philadelphia in 1907. Two years later he entered the Army of the United States as a First Lieutenant in the Medical Corps. Training followed in the Army Medical School and in the Medical Field Service School at Carlisle, Pa. Colonel Cooper's special interest was tuberculosis.

While in Puerto Rico, Colonel Cooper, until his retirement, was Medical Chief of the Rodriguez General Hospital. His efforts were instrumental in securing PWA funds for the reconditioning of this hospital and its restoration to its present state as an excellent example of true Spanish architecture of colonial days. In 1940 he joined the staff of the School of Tropical Medicine, where his services as liaison officer between this institution and the U. S. Army in Puerto Rico during the trying days of World War II are still remembered. Colonel Cooper was a member of the medical staffs of the University and Presbyterian Hospitals, of San Juan.

Colonel Cooper was a diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians since 1930 and of the American Medical Association; and a member of the American Academy of Tuberculosis Physicians, Association of Military Surgeons of the United States, Association of Medical Veterans of World War I, and Puerto Rico Medical Association. He was also a member of the Society of the Sons of the American Revolution.

P. Morales Otero, M.D., F.A.C.P.

DR. WILLIAM R. GALBREATH

Dr. William Robert Galbreath, an Associate of the College, died in San Antonio, Tex., on January 6, 1949, at the age of 37. Tragically, death occurred suddenly due to coronary occlusion after he had successfully combatted a tuberculous infection contracted while he was on military duty overseas.

Dr. Galbreath was born in Shreveport, La., where he spent his boyhood and received his early education. He held the B.S. degree from Centenary College, and M.S., M.B. and M.D. degrees from Louisiana State University. In 1942, he completed a three-year residency in medicine at the Charity Hospital of Louisiana, New Orleans, was elected to associateship in the College, and volunteered for service in the Army of the United States, affiliating with the 64th General Hospital Unit sponsored by the Louisiana State University School of Medicine. He served with distinction in the Mediterranean Theatre until he became ill in 1944, rising from the rank of first lieutenant to that of major.

Following separation from the Army and during the period of his convalescence, he held appointment and gave valuable service as Clinical Instructor in Medicine at Louisiana State University, and later as Associate in the Gilmer Chest Hospital of Shreveport. In 1948, his pulmonary lesion apparently cured, he was appointed Chief of the Tuberculosis Service in the Veterans Administration Hospital at Jackson, Miss., a post which he occupied at the time of his death.

Dr. Galbreath's friends and colleagues will remember him as an accomplished and talented musician, a capable and conscientious physician, a gentleman in the fullest sense of the word. May he rest in peace.

Edgar Hull, M.D., F.A.C.P.,
Governor for Louisiana

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